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Progresses on the development of stereoselective [2+2], [2+3] and [4+3] cycloadditions.

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Progresses on the development of stereoselective [2+2], [2+3] and [4+3] cycloadditions

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By

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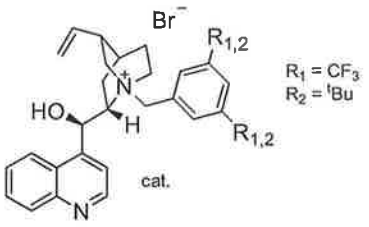
"Science is always imperfect.
Every time you solve a problem,
creates a least ten new."

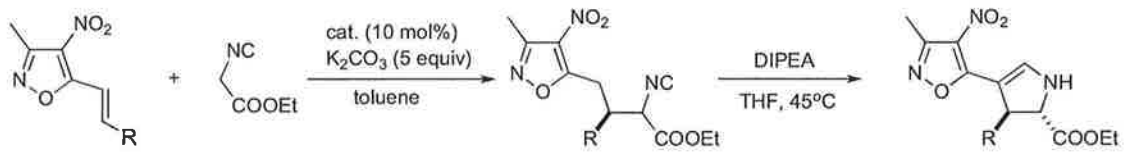
George Bernard Shaw

Abstract

The present work dealt with the preparation of some key intermediates and their use for the generation of chemical diversity.

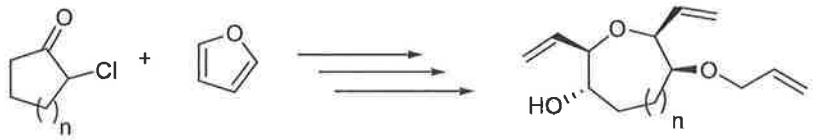
In **Chapter 2** we described a Catalytic Asymmetric Conjugate Addition of isocyanoacetates to 4-nitro-5-styrylisoxazoles.



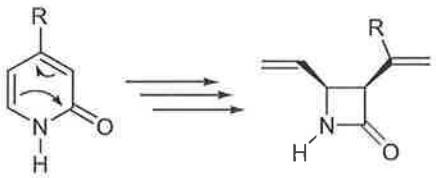


2.17a-n **2.18** **2.19a-n** **2.20a-n**

In **Chapter 3** we described a new strategy for the preparation of medium sized oxepanes oxocanes and oxonanes.



In **Chapter 4** we described a novel route to alkene-functionalised monobactams and their potential in diversity oriented synthesis is still in progress.



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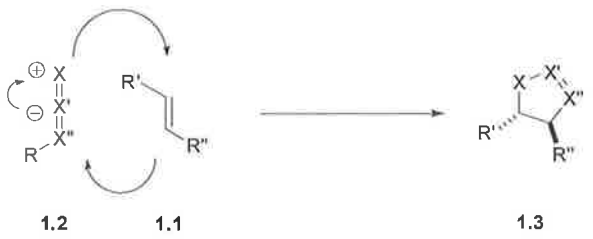
Chapter 1: [4 + 3] and [3 + 2] Cycloadditions: Application to the synthesis of biologically active natural products.

1.1 Introduction.

[n + m] Cycloaddition reactions represent one of the most powerful methods used to access bridge-containing organic compounds, particularly those of natural origin.
This review summarizes the application of [4 + 3] (covering period 2006-2011) and of [3 + 2] cycloadditions (covering period 2000-2011) in natural products synthesis. We have equally reviewed the [3 + 2] cycloadditions occurring *via* the classic 1,3 dipolar mechanism as well as those [3 + 2] occurring in step-wise *unclassical* fashion. Similarly we have reviewed those [4 + 3] cyclization catalyzed by transition metals, those 1,3 dipolar cycloadditions involving oxyallyl cations and finally step-wise [4 + 3] intramolecular cycloadditions.

1.2 [3 + 2] Cycloaddition Reaction.

[3 + 2] dipolar cycloadditions are known as the Huisgen cycloaddition. These reactions lead to five-membered (hetero)cycles **1.3** starting from a dipolarophile **1.1** (2 π-electrons) and a 1,3-dipolar compound **1.2** (4 π-electrons) through a concerted, pericyclic mechanism (**Scheme 1**).



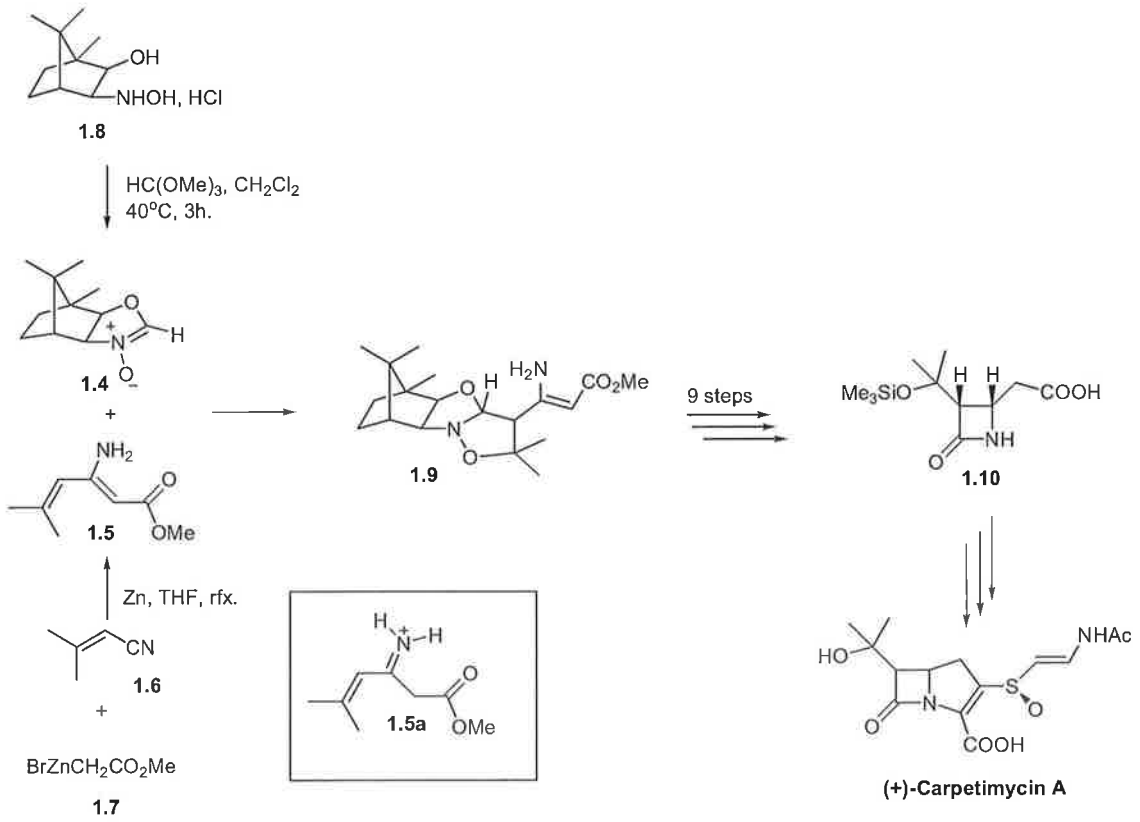
1.2 1.1 1.3

Scheme 1.

1.2.1 1,3-Dipolar Cycloaddition of Nitrone intermediates.

Nitrones are very useful intermediates in [3 + 2] cycloadditions which react with different dipolarophiles. In 2000 Langlois and co-workers accomplished a formal stereoselective synthesis of (+)-Carpetimycin A using a new asymmetric [2 + 3] cycloaddition.[1] Carpetimycin A was isolated from fermentation broth of *Streptomyces* sp. KC-6643; this compound exhibited a strong activity against Gram-positive and Gram-negative bacteria and showed a good resistance to β-lactamase-producing strains.[2]

The key step of the synthesis was the cycloaddition between **1.5** and **1.4**, the latter obtained by condensation of hydroxylamino isoborneol hydrochloride **1.8** with trimethyl orthoformate, whereas dipolarophile **1.5** was prepared by condensation between reagents **1.7** and **1.6**.



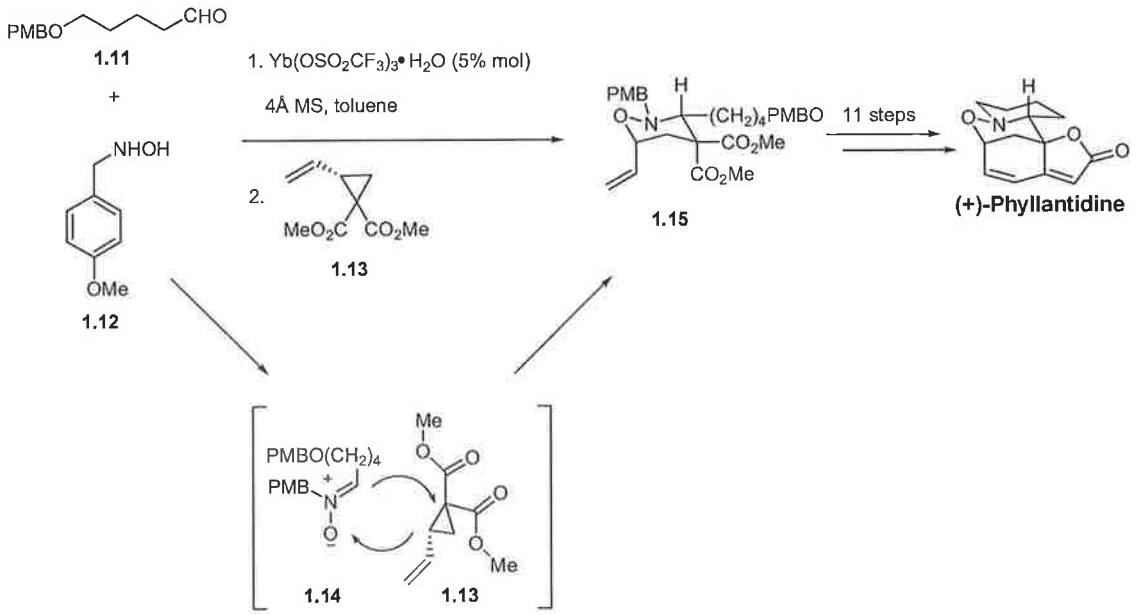
Scheme 2.

The reaction proceeded smoothly at 40°C and afforded a single adduct **1.9** in 52% yield (**Scheme 2**). The high reactivity of dipolarophile **1.5** in which a trisubstituted double bond is engaged in cycloaddition is worthy of note. Since hydroxylamino isoborneol **1.8** was used as its hydrochloride, a possible equilibrium between this salt and dipolarophile **1.5** could lead to the more reactive iminium **1.5a**.

Starting from **1.9** the β-lactam derivate **1.10** was obtained in nine steps. Compound **1.10** served as a synthetic precursor of Carpetimycin A.

In 2007 Carson and Kerr reported[3] the total synthesis of (+)-Phyllantidine, a natural product isolated from *Phyllanthus discoides* and *Securinega suffruticosa*.[4] The key C-C forming step involved a $Yb(OTf)_3$-mediated [3 + 2] cycloaddition of nitrones.

The synthesis started from *p*-methoxybenzyl hydroxylamine **1.12** and aldehyde **1.11** which reacted in toluene in the presence of 5 mol% of $Yb(OTf)_3$ and 4 Å molecular sieves (**Scheme 3**) to give nitrone **1.14**. Once formed **1.14** was subsequently reacted with homochiral cyclopropane **1.13**. The adduct **1.15** was obtained as the major diastereomer (12 : 1, *cis : trans*) and in 80% enantiomeric excess (*ee*) . Compound **1.15** was thereafter elaborated to give (+)-Phyllantidine in eleven successive steps.

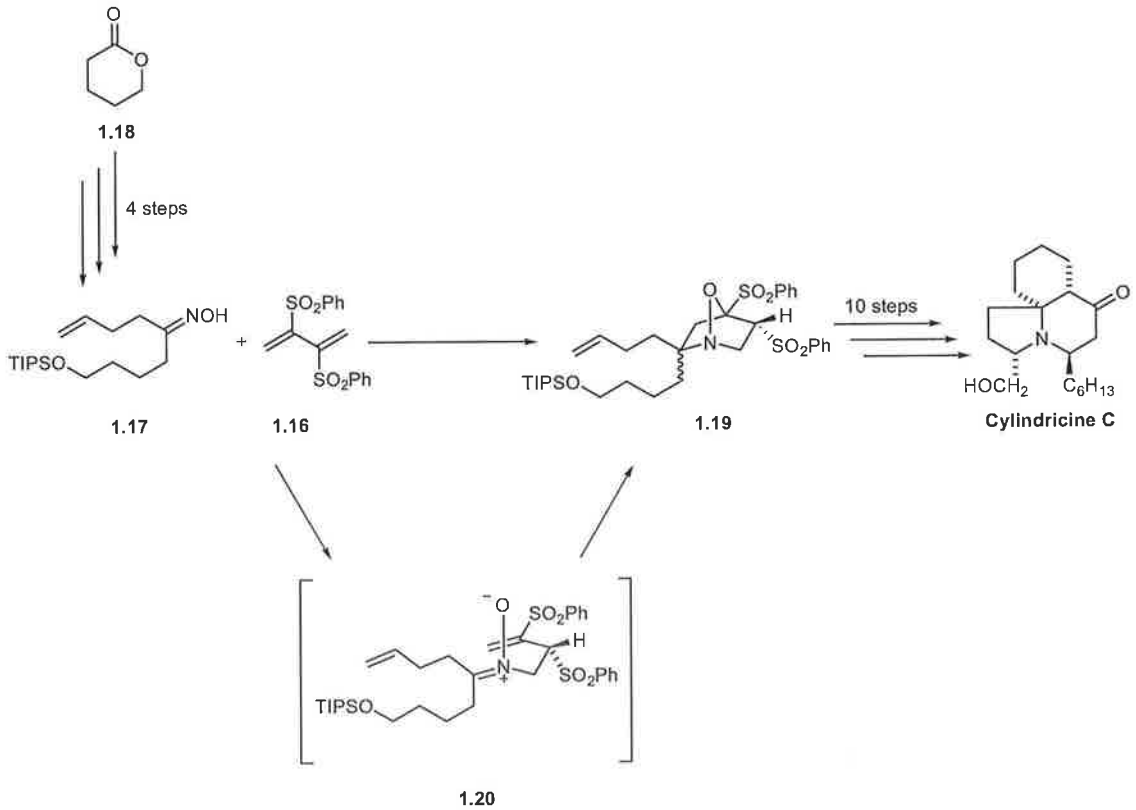


Scheme 3.

In 2008 Padwa used a new approach[5] for the synthesis of the marine alkaloid (±)-Cylindricine C, an intriguing target member of an alkaloid family isolated by Blackman and co-workers from the ascidian *Clavelina cylindrica* in the early 1990s.[6]

The key element of the synthesis consisted of a Michael addition/dipolar cycloaddition cascade of **1.16** and **1.17**, prepared from *δ*-valerolactone **1.18**. The mixture was heated at 90°C in $CHCl_3$ to afford the expected cycloadduct **1.19** as a 1:1 mixture of diastereomers in 75% yield, which gave Cylindricine C in ten steps.

The formation of the bicyclic isoxazolidine **1.19** involved conjugate addition of the oxime to the activated diene **1.16** to give a transient nitrone **1.20** which then underwent a subsequent intramolecular 1,3-dipolar cycloaddition with the adjacent vinyl sulfone (**Scheme 4**).

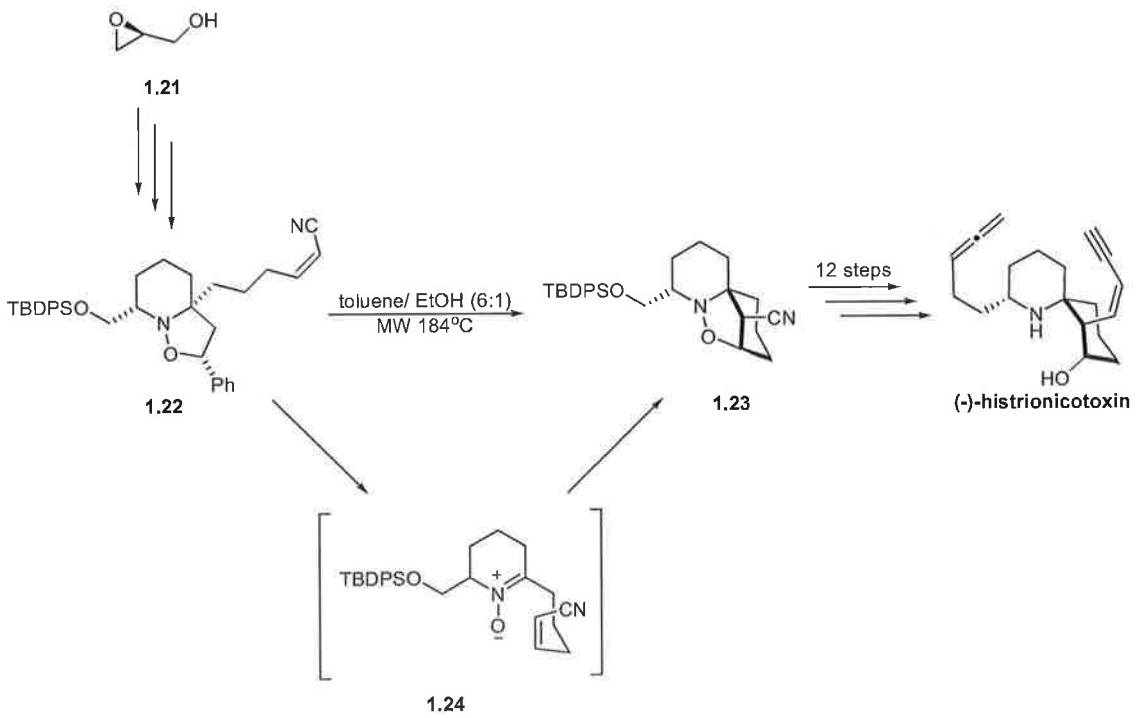


Scheme 4.

In the same year, Holmes' group achieved the total synthesis of (-)-Histrionicotoxin 285A using a [3 + 2] cycloaddition as the key step.[7]

The Histrionicotoxins (HTXs) are a family of spirocyclic piperidine alkaloids isolated in 1971 from the Colombian frog *Dendrobates histrionicus*.[8] Their intriguing molecular architecture coupled with potent inhibition of the nicotinic acetylcholine receptor[9] has made them attractive targets for total synthesis.

The [3 + 2] cycloaddition took place when nitrile **1.22** was subjected to a microwave (MW) induced 1,3-dipolar cycloreversion to **1.24** (with accompanying extrusion of styrene) followed by an intramolecular cycloaddition process under thermodynamic control to furnish the required (6,6,5)-tricycle **1.23** (**Scheme 5**).[10] Starting from compound **1.23**, the synthesis of (-)-Histrionicotoxin 285A was accomplished in twelve steps.

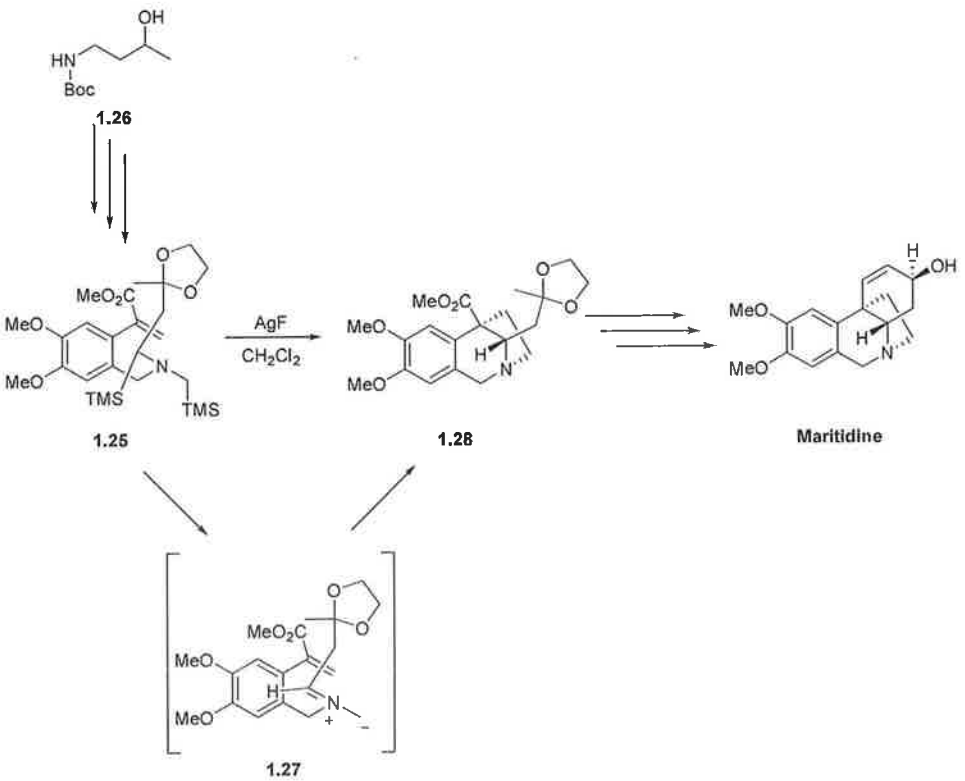


Scheme 5.

1.2.2 1,3-Dipolar Cycloaddition of Azomethine intermediates.

1,3-Dipolar cycloaddition of azomethine ylides, generated *in situ*, is a useful method for the construction of *N*-containing heterocycles. Recently Pandey and co-workers reported[11] a total synthesis of Maritidine, isolated from *Pancratium maritimum*, *Pancratium tortuosum*, and *Zephyranthes* Genera.[12] The vicinal quaternary and tertiary stereocenters of the 5,10b-ethanophenanthridine skeleton were created in a single step by an intramolecular [3 + 2]-cycloaddition of a non-stabilized azomethine ylide as the key step.

The cycloaddition reaction was performed by addition of **1.25**, synthesized from **1.26**, to a mixture of Ag(I)F in dry DCM. The reaction conferred the desired cycloadduct **1.28** in 56% isolated yield through the non-stabilized azomethine ylide **1.27**, generated *in situ* by removal of two TMS groups (**Scheme 6**).



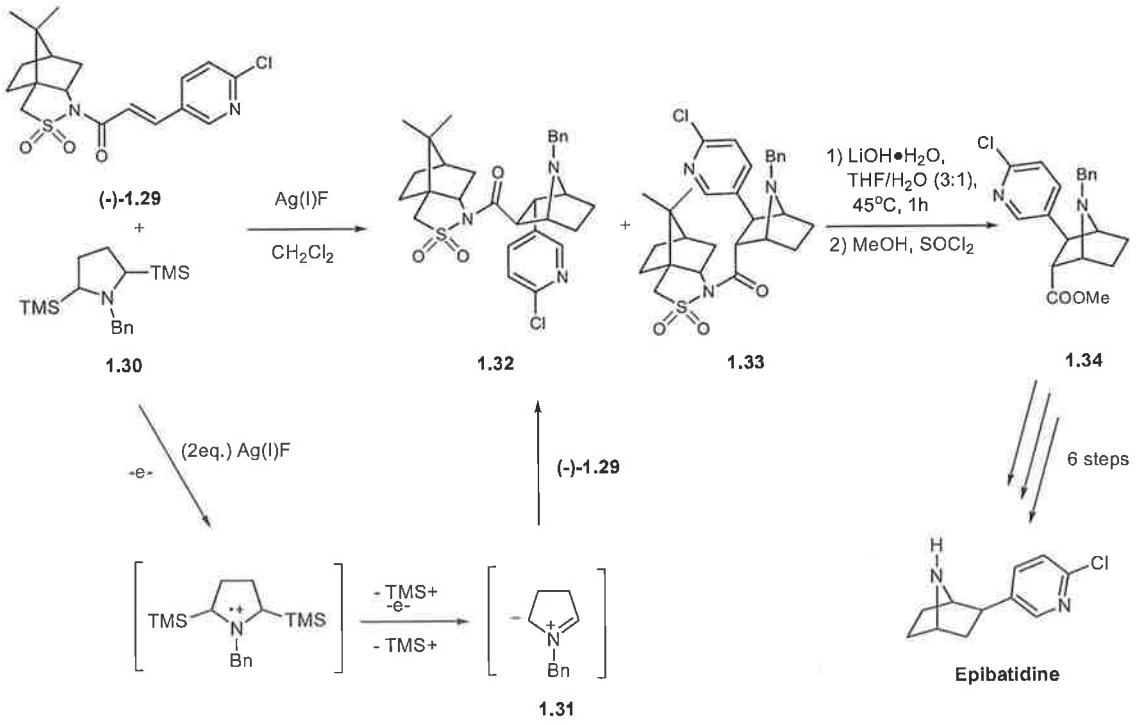
Scheme 6.

From compound **1.28** Maritidine was synthesized in six steps.[13]

Epibatidine is a further example of natural product synthesized *via* [3 + 2]-cycloaddition of non-stabilized cyclic azomethine ylides.[14] Epibatidine is an alkaloid found in the skin of the Ecuadorian neotropical poisonous frog, *Epipedobates tricolor* in 2002. It was initially isolated by John Daly at the National Institute of Health in 1992, and was found to be a powerful analgesic, 200-500 times the potency of morphine with a non-opioid mode of action.[15] In order to prepare enantiopure Epibatidine, a chiral dipolarophile **(-)-1.29** was synthesized by a novel Heck-coupling reaction.[16]

A [3 + 2]-cycloaddition reaction of cyclic non-stabilized azomethine ylide (AMY) **1.31,** generated from **1.30** in presence of 2 equiv. of AgF, with compound **1.29** gave two cycloadducts **1.32** and **1.33** with good exo : endo selectivity (9 : 1) as shown in **Scheme 7.**

The conversion of **1.34** to epibatidine was accomplished in six successive steps.



Scheme 7.

1.2.3 1,3-Dipolar Enantioselective Cycloadditions.

In 2010 Reisman and co-workers found an enantioselective synthesis of pyrroloindolines by a formal [3 + 2] cycloaddition reaction[17] that is expected to facilitate the total synthesis of pyrroloindoline alkaloids. Alkaloids shown in **Figure 1** are an important class of natural products that were isolated from a widespread series of natural sources, including amphibians, plants, and marine algae. First described in the late 1930s, this alkaloid family exhibits remarkable biological properties, including anticholinesterase,[18] anti-inflammatory,[19] and anticancer activities.[20]

A formal [3 + 2] cycloaddition reaction between C(3)-substituted indole **1.35** and 2-amidoacrylate **1.36** was catalyzed by 20 mol % of (*R*)-BINOL and 1.2 eq. of $SnCl_4$ in DCM to provide pyrroloindoline **1.37** (**Scheme 8**).

Compound **1.37** was isolated in 86% yield as a 4:1 mixture of *exo* and *endo* diastereomers, which are formed in 94% and 91% *ee* respectively.

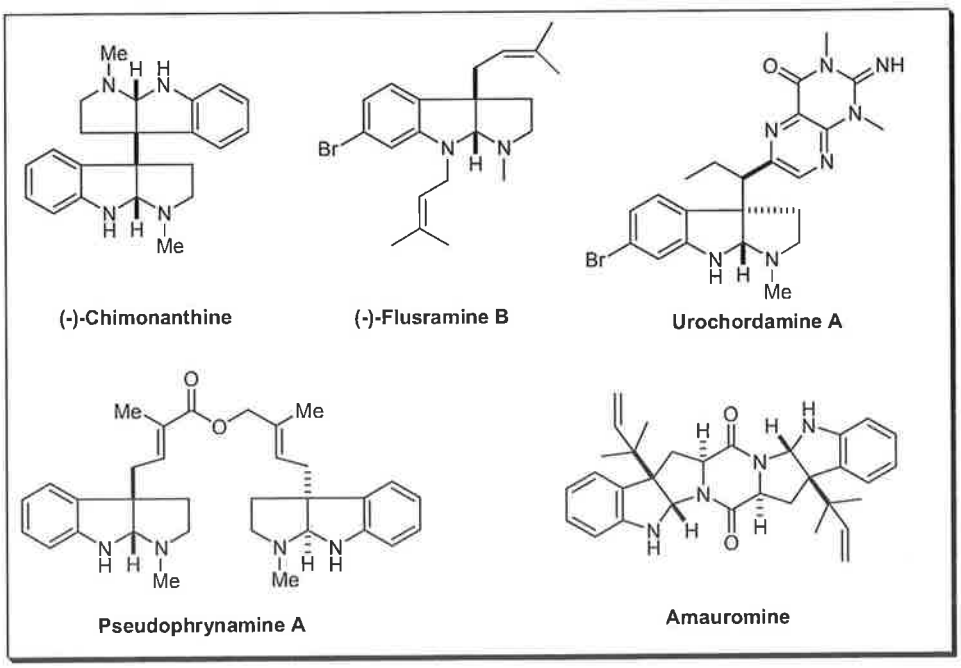
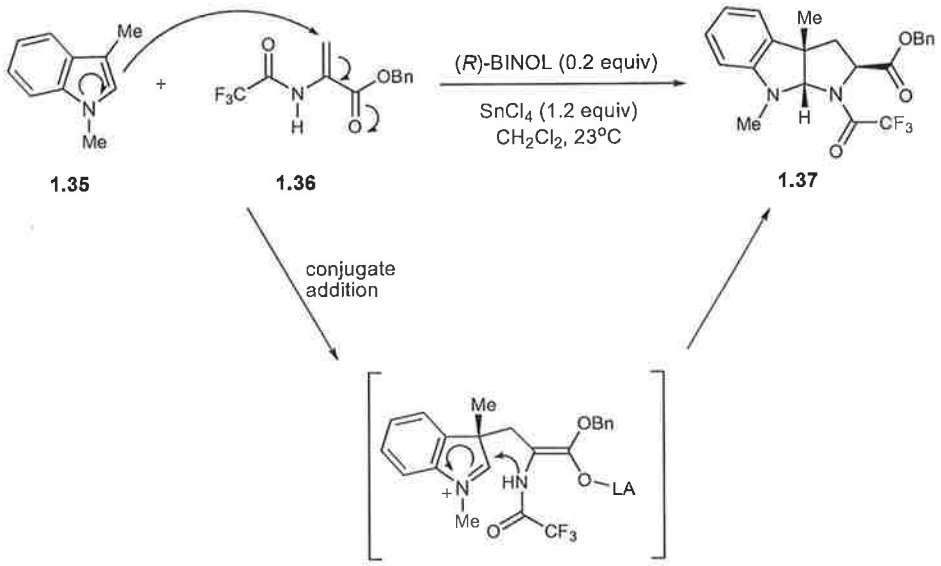


Figure 1.



Scheme 8.

Another application was reported in 2007 from Ishihara and coworkers who synthesized an optically active compound as an intermediate candidate in the enantioselective total syntheses of 4α-methylhydrofluorene diterpenoids such as (-)-Taiwaniaquinol B through a useful formal [2 + 3] cycloaddition.[21] Taiwaniaquinol B was isolated from *Taiwania cryptomerioides*, a common Taiwanese pine tree. The biochemistry of this family of diterpenoids has not been examined comprehensively yet, but aromatase inhibitory activity has been identified for standishinal, which could lead to the development of valuable therapeutic agents in the treatment of estrogen-dependent cancers.[22]

They described a novel useful formal [2 + 3] cycloaddition of **1.38** and **1.39** by an organocatalytic enantioselective [2 + 2] cycloaddition and subsequent ring expansion to give optically active **1.42** with high *ee*. The [2 + 2] cycloaddition reaction of compound **1.39** with **1.38** was performed in the presence of 20 mol % of **1.40** and $C_3F_6S_2O_4NH$ as Brønsted acids in nitropropane at -20°C to give **1.41** in 24% yield and 90% *ee* (**Scheme 9**).

Initially, the enantioselective Michael addition of alkenes to a (*Z*)-iminium intermediate, should occur through enantiofacial approach between the *re* face of electron-rich alkenes

and the *si* face of the electron-deficient (*Z*)-iminium intermediate in an extended transition-state assembly TS-**9** (**Figure 2**).

The (*Z*)-iminium isomer of **9** is expected to be more stabilized by intramolecular hydrogen-bonding interactions between R_2-C=O or *o*-F substituents in R_2 and H-$N^+(CH_2CH_2)_2$. Subsequently, the resulting tertiary carbocation intermediate would be intramolecularly cyclized through a folded TS-**10**.

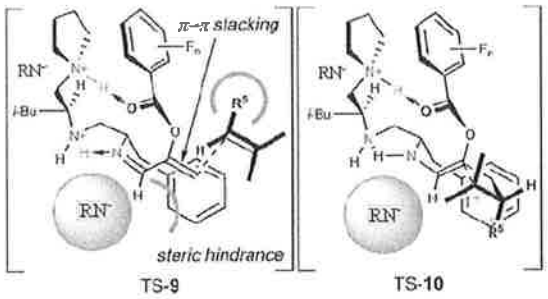
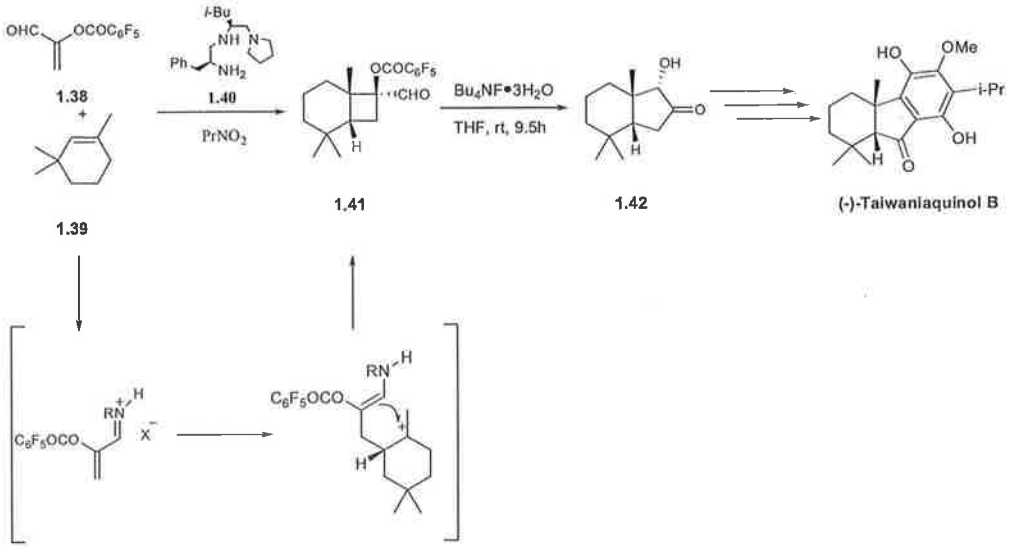


Figure 2.

Compound **1.41** was succesfully expanded to 2-hydroxycyclopentanone **1.42** which could become a new chiral common intermediate candidate in the enantioselective total syntheses of 4a-methylhydrofluorene diterpenoids such as (-)-Taiwaniaquinol B.[23,24]

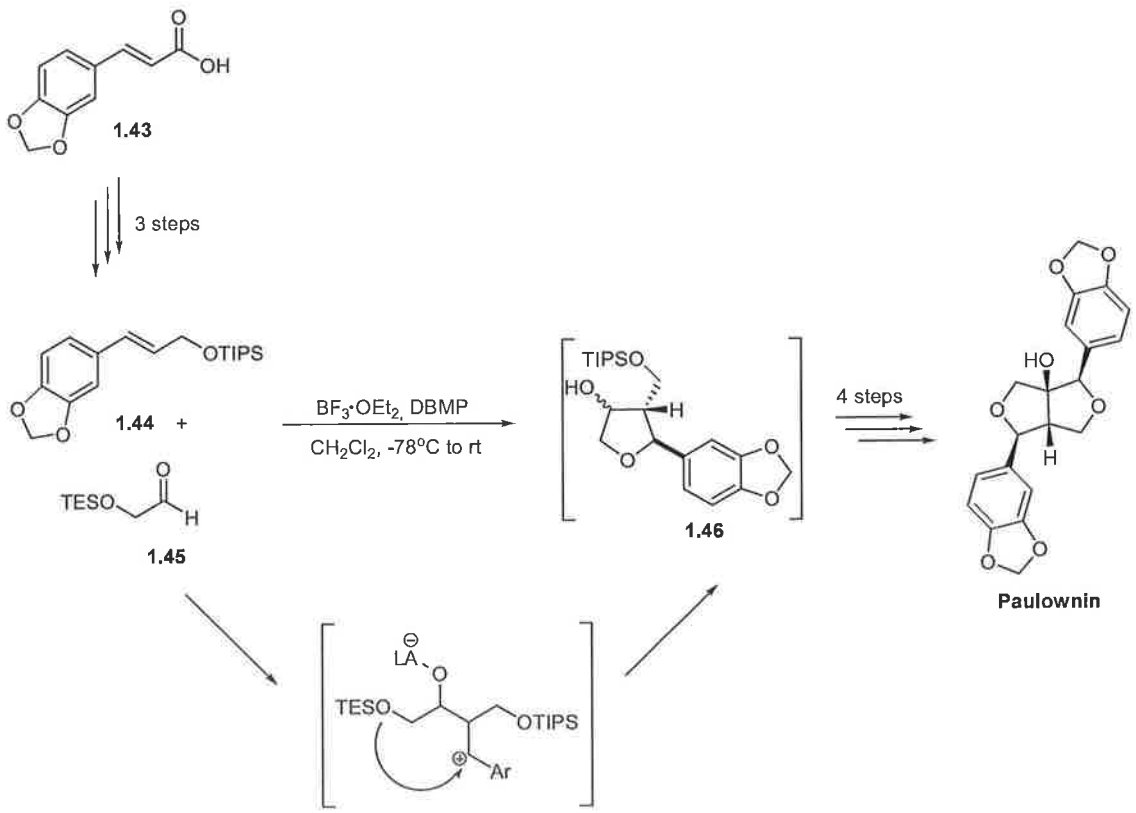


Scheme 9.

1.2.4 1,3-Dipolar Cycloaddition in presence of Lewis Acid.

In 2008 Angle's group reported a formal Lewis acid mediated [3 + 2]-cycloaddition[25] applied to the total synthesis of the naturally occurring furofuran lignan (±)-Paulownin which was isolated from *Paulonia tomentosa* (kiri) by Takahashi in 1963. Paulownin and similar compounds are attractive synthetic targets due to their antioxidant properties and other biological activity.[26]

The synthesis started from the commercially available 3,4-(methylenedioxy)cinnamic acid **1.43** which was converted into compound **1.44** in three steps with excellent yield (**Scheme 10**).



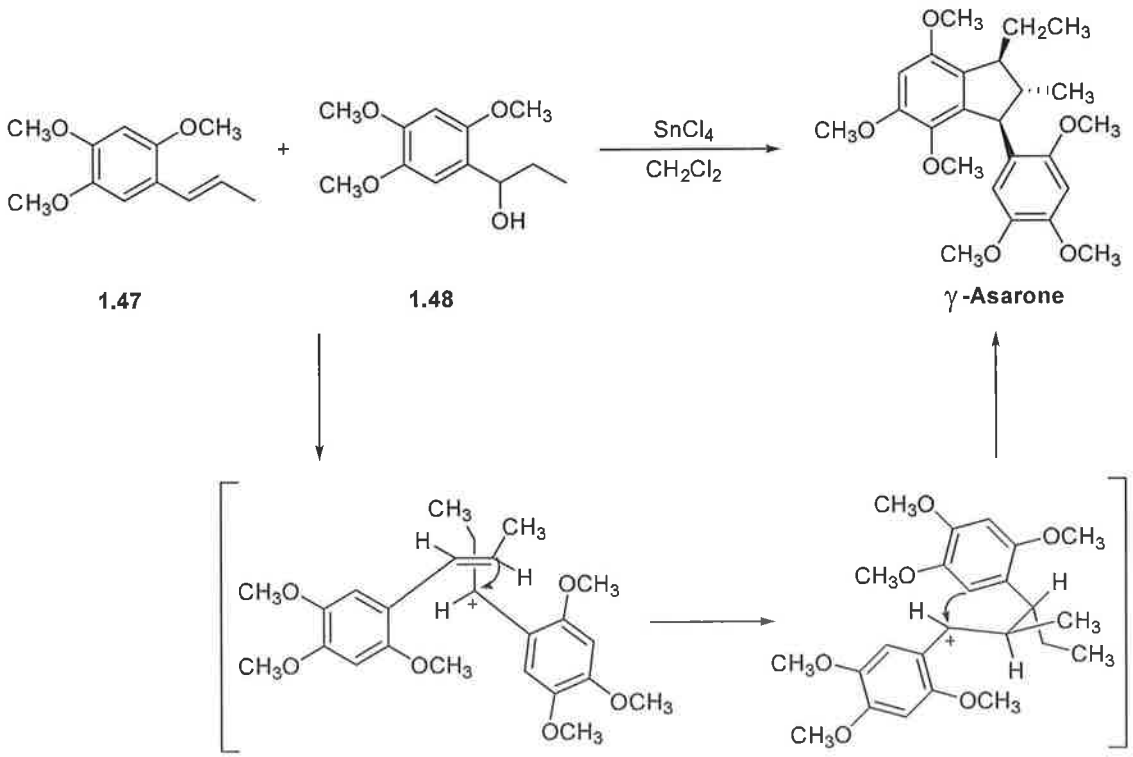
Scheme 10.

The cycloaddition between 2.0 equiv. of **1.44** and **1.45** was performed in presence of 1 equiv. of $BF_3{\cdot}Et_2O$ and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP), to give compound

1.46 in 74% yield as a mixture of two diastereomers (3:1 ratio). The mixture of diastereomers was used without further separation leading to Paulownin in a four step synthesis.

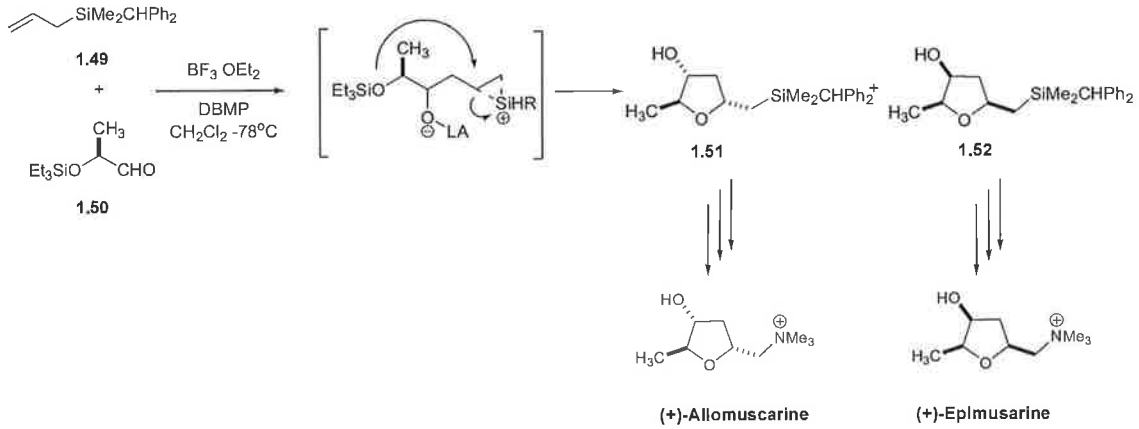
In 2003 γ-Asarone was synthesised in Moltrasio's laboratory.[27] Asarone was originally isolated from the essential oil of *Acorus calamus* which is known as an insect growth regulator,[28a] fungicide, insecticide,[28b] sedative and hypothermic agent.[28c]

The synthesis of the indane structure was performed via formal [3+2] cycloaddition between **1.47** and **1.48,** catalysed by $SnCl_4$ affording γ-Asarone in 40% yield (**Scheme 11**). Noteworthy γ-indane was obtained unexpectedly over the α-one and this could be explained by the presence of two methoxy groups in 2 and 5-positions in the starting alcohol.



Scheme 11.

Angle's group reported in 2002 a total synthesis[29] of the muscarine alkaloids (-)-Allomuscarine and (+)-Epimuscarine, which were first isolated from *Amanita muscaria*, a mushroom found in pinewoods. (-)-Allomuscarine and (+)-Epimuscarine act on the peripheral nervous system causing lowering of blood pressure, slowing of heart rate and bronchial constriction. The key step of the synthesis was a [3+2]-cycloaddition of allylsilane **1.50** and the protected lactic aldehyde **8 (Scheme 12)**. The reaction was performed under the catalysis of $BF_3 \cdot Et_2O$ at -78°C to ensure complete consumption of the aldehyde. The acid scavenger, DBMP, was added to minimize the decomposition of the aldehyde and allylsilane under the long reaction times. Compound **1.50** provided cycloadducts **1.51** and **1.52** in 80% yield and 2.2 : 1 ratio.

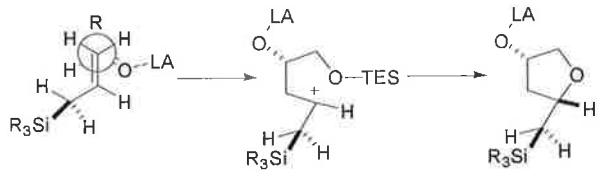


Scheme 12.

The mechanism of this reaction involves the addition of the allylsilane to the aldehyde which is activated by the Lewis acid (**Scheme 13**). The results indicate that the triethylsilyl ether oxygen is more nucleophilic than the alkoxide when in a complex with a Lewis acid and thus it is the internal nucleophile that participates in the cyclization. In this work both diastereomers were observed with the major isomer having the same *cis* orientation between the C-3 hydroxyl and C-5 silyl methylene substituent. This behaviour was observed in the case of tetrahydropyrans. This selectivity can be explained by an overall *cis* addition of the electrophile and nucleophile across the double bond of the olefin.[30] The introduction of a methyl-substituent on the aldehyde provided a facial

selectivity (Felkin-Anh) of the addition of the allylsilane. The *R*-methyl aldehyde **1.50** showed a low Felkin-Anh selectivity and a mixture of products was observed in this case. It is possible that there was more to the stereoselectivity than just simple Felkin-Anh control. In this case, the Felkin-Anh selectivity was compromised, but the 3,5-*cis* selectivity was complete. Both diastereomers had the hydroxyl group in a *cis* orientation to the silyl methylene substituent. The difference in the stereochemistry between the major and the minor diastereomers was in the orientation of the methyl group relative to the hydroxyl group: *trans* in the major diastereomers (**1.51**) and *cis* in the minor diastereomers (**1.52**).

The size of the substituents on silicon affected the diastereomeric ratio of the tetrahydrofuran products; an increase in the size of the substituents on silicon resulted in an enhancement in the diastereomeric ratio of the products.



Scheme 13.

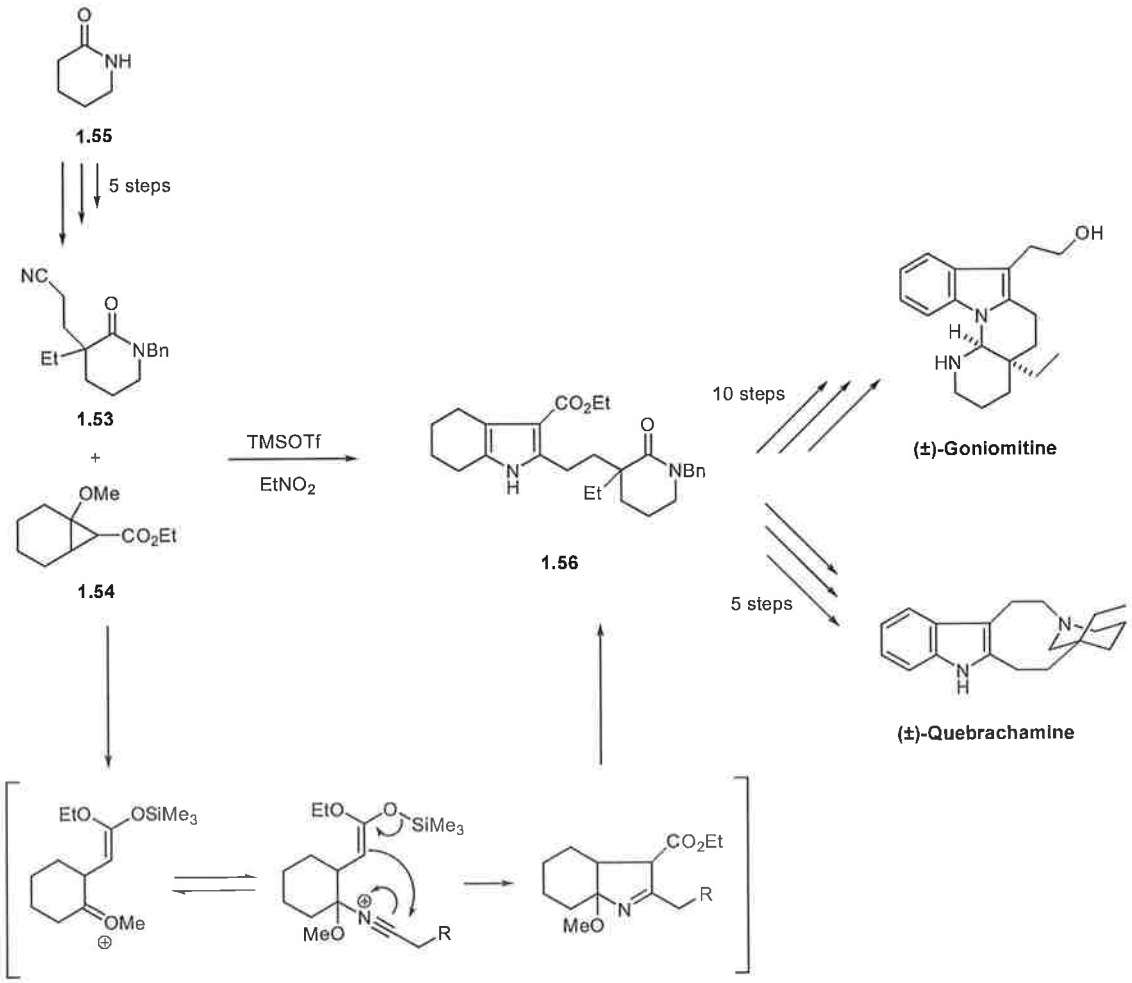
1.2.5 1,3-Dipolar Cycloaddition via formal nitrile/Donor-Acceptor cyclopropane.

Pagenkopf and co-workers perfomed the total synthesis of (±)-Goniomitine in 2008 and later the total synthesis of (±)-Quebrachamine via a formal nitrile/Donor-Acceptor (DA) cyclopropane [3 + 2] cyclization.[31] These indole alkaloids are members of the aspidosperma family of natural products. (±)-Goniomitine was isolated in 1987 from the root bark of *Gonioma malagasy* by Husson and co-workers;[32] this compound showed weak cytotoxicity (IC_{50} = 7.1 μM) toward L1210 leukemia cells in culture.[33] Quebrachamine was first isolated over a century ago by Hesse from Aspidosperma quebracho tree bark and it showed diverse biological activity,[34] including α-adrenergic blocking behaviour in urogenital tissue.[35] The highlight of the synthesis includes the first application of a formal [3 + 2] cycloaddition between a highly functionalized nitrile **1.53,**

obtained from **1.55,** and donor- acceptor cyclopropane **1.54** in presence of 1.05 equiv of Me_3SiOTf in $EtNO_2$ at -30°C to give the tetrahydroindole adduct **1.56** in 74% yield.

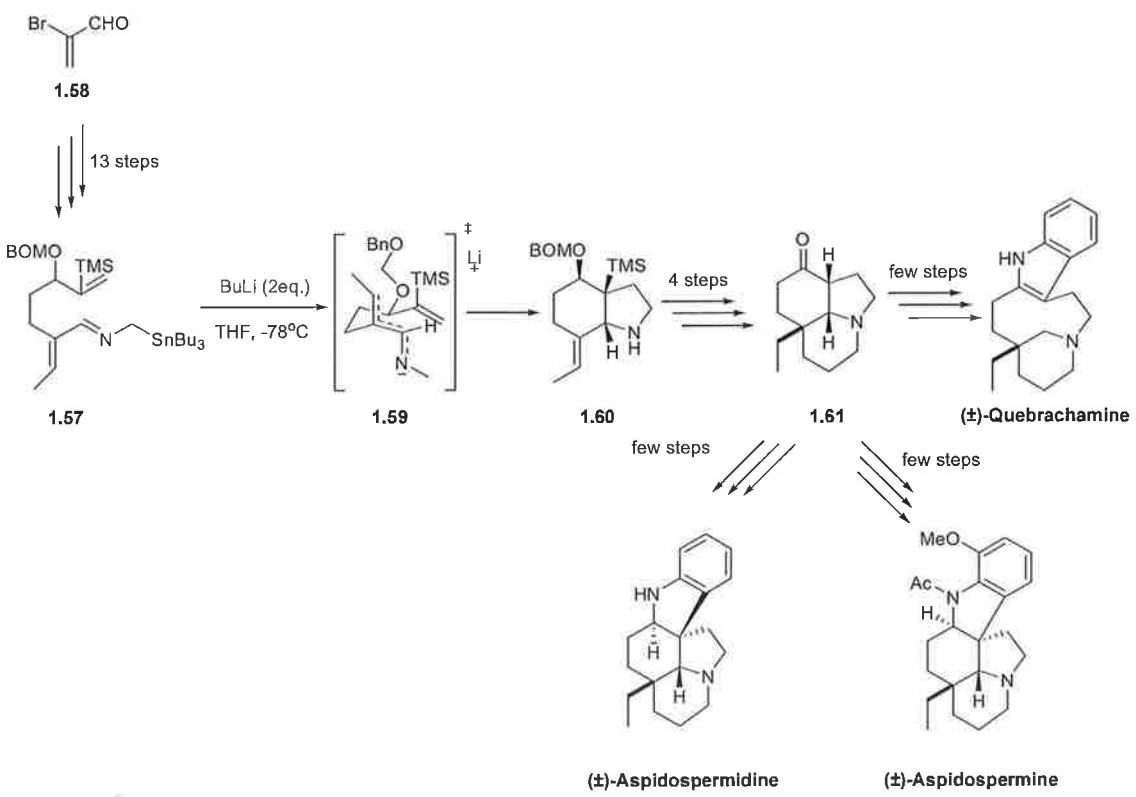
A plausible mechanistic pathway for this key step likely involves the nitrilium ion intermediate formed in a Ritter-like process by attack on the oxocarbenium ion. The reversible nature of the nitrile addition is supported by the divergent stereochemical outcomes of allylation reactions and nitrile annelations of carbohydrate-derived cyclopropyl lactones.

Starting from **1.55,** (±)-Goniomitine was obtained in fifteen steps with an overall yield of 5%, whereas (±)-Quebrachamine, was synthesised from **1.56** in five linear steps and 18% overall yield.



Scheme 14.

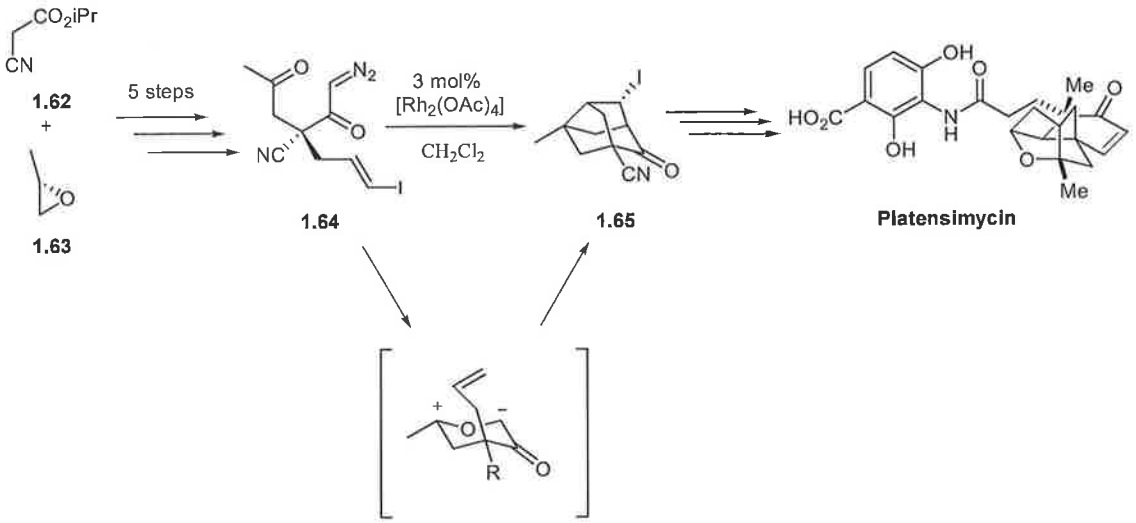
Quebrachamine was even synthesised in Pearson's laboratory in 2006.[36] The *Aspidosperma* alkaloids (±)-Quebrachamine, (±)-Aspidospermidine and (±)-Aspidospermine were completed by intercepting the classic Stork-type intermediate **1.61** (**Scheme 15**).[37] The key step of the sequence involved an intramolecular [3 + 2] cycloaddition of the 2-azapentadienyllithium chair transition state **1.59** in which the anion exists in the extended all-"W" conformation. Intermediate **1.59** which was formed *in situ* from the corresponding imine **1.57,** obtained in thirteen steps from **1.58**, adding a dilute solution of *n*-butyllithium in THF at -78°C providing **1.60** as the only diastereomer because of the presence of trimethylsilyl group previously included (**Scheme 15**).



Scheme 15.

In 2008 Eun Lee and co-workers prepared a carbonyl ylide cycloaddition approach [38] to Platensimycin (**Figure 16**), a metabolite of *Streptomyces platensis* that has potent activity against Gram-positive bacteria, including multiresistant strains of staphylococci and enterococci. A [3 + 2] cycloaddition was performed on compound **1.64** (**Scheme 16**),

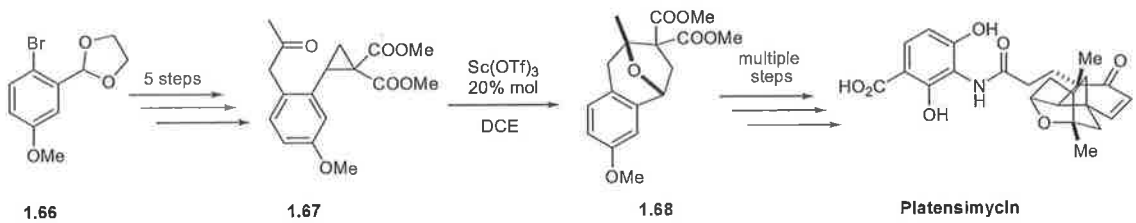
obtained by the reaction between **1.62** and **1.63** in 99% *ee*, in the presence of 3 mol% of rhodium(II) acetate to afford **1.65** in 83% yield. This approach may be easily adapted for the synthesis of Platensimycin analogues.



Scheme 16.

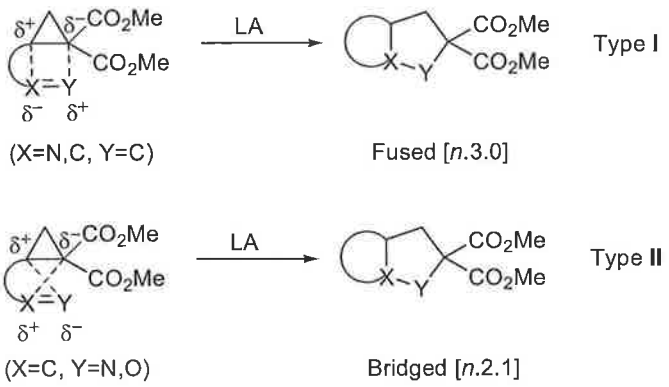
Later in 2010, Wang and co-workers reported the construction of a bridged oxa-[3.2.1] skeleton **1.68**,[39] as precursor of Platensimycin[40], through intramolecular [3 + 2] cycloaddition of cyclopropane 1,1-diester **1.67**, prepared in five steps from **1.66**, using 20 mol % $Sc(OTf)_3$ as catalyst in 1,2-dichloroethane in 87% yield (**Scheme 17**).

Coumpound **1.68** could be additionally converted into Platensimycin using the method reported by Njardarson [41b] and Nicolaou. [41a]



Scheme 17.

Compared to the Lewis acid catalyzed intermolecular [3 + 2] cycloadditions of cyclopropane 1,1-diester, the intra-molecular variant has been less exploited despite showing promising potential for the synthesis of natural products. The intramolecular [3 + 2] cycloaddition can be classified into two categories: formation of a fused bicyclic [*n*.3.0] skeleton (type I) and a bridged bicyclic [*n*.2.1] skeleton (type II) as shown in **Scheme 18**.

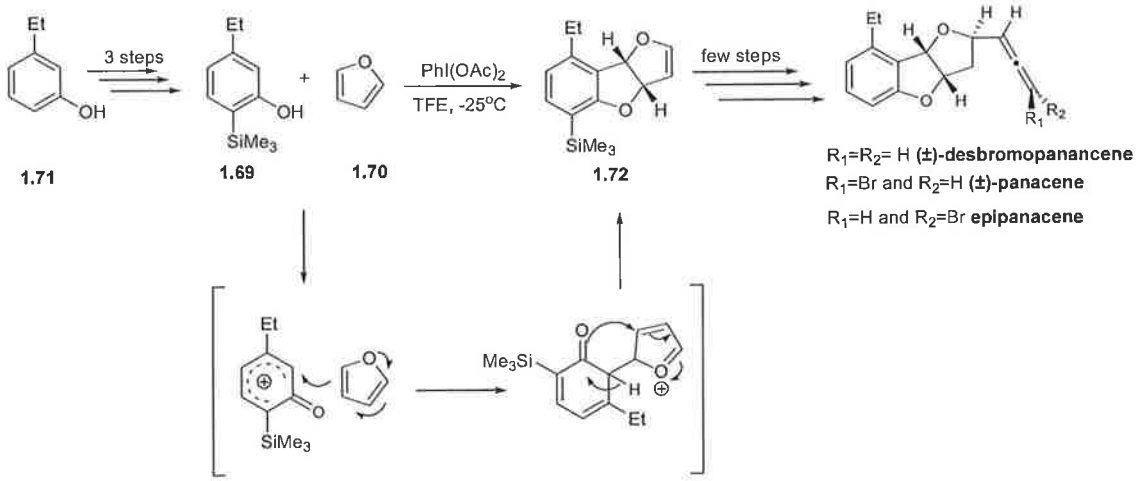


Scheme 18.

1.2.6 1,3-Dipolar Cycloaddition in presence of Oxidant agent.

In 2008 Canesi's group introduced an oxidative [2+3] cycloaddition between substituted phenol and furan[42] as a precursor of the synthesis of the marine (±)-Panacene and terrestrial (±)-Desbromopanacene. (±)-Desbromopanacene is a plant metabolite isolated in 1915 from *Panax ginseng* and *Panax quinquefolius*.[43] Panacene was isolated in 1977 by Meinwald and co-workers from *Aplysia brasiliana*, a sea hare indigenous to the gulf coast of Florida. Panacene has shark antifeedant properties, and it is thus believed to protect the sea hare from predatory fish. These syntheses were based on the umpolung of the aromatic ring. Compound **1.69** was obtained in three steps from **1.71** (**Scheme 19**). Compound **1.72** was afforded by treatment with iodobenzene diacetate (DIB) as the oxidant in presence of furan **1.70** in TFE at -25°C for 1 minute. The TMS group on **1.69** was introduced because it blocks position 6 of the phenol and forces the subsequent

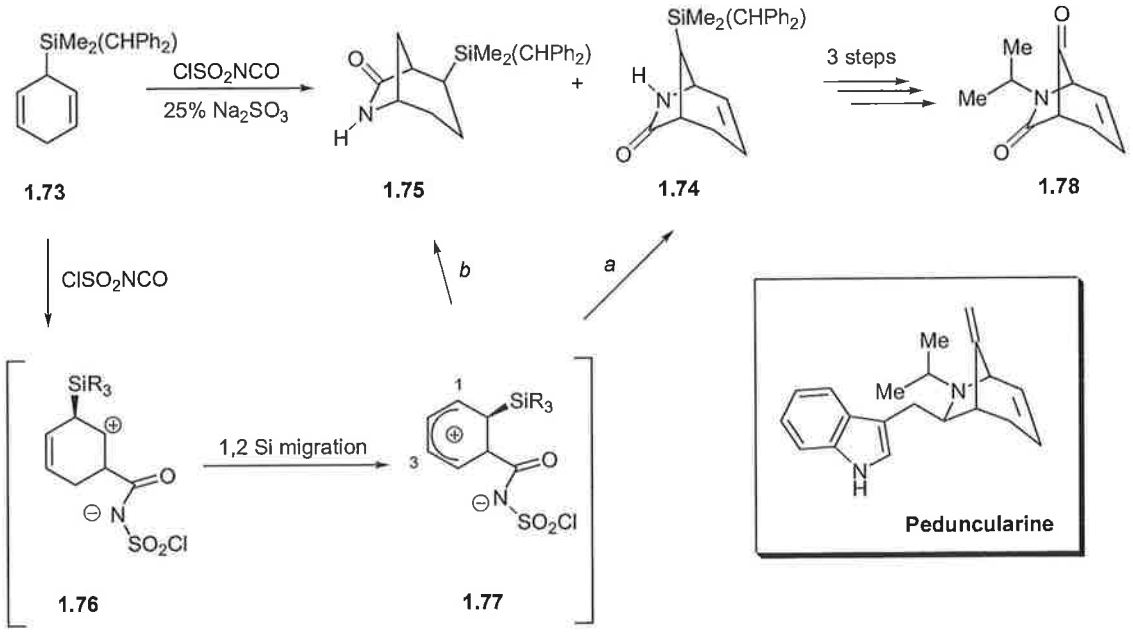
oxidative annulation sequence to occur exclusively at position 2. From compound **1.72,** (±)-Desbromopanacene was synthesised in two steps and 20% overall yield, Epipacene in four steps and 14.3% overall yield and (±)-Panacene in four steps from **1.71.**



Scheme 19.

1.2.7 1,3-Dipolar Cycloaddition.

The alkaloid (±)-Peduncularine, which was first isolated in 1971,[44] is the principal alkaloid of the Tasmanian shrub *Aristotelia peduncularis*.[45] The interest in Peduncularine has been stimulated by the combination of its anticancer activity and the presence of an unusual 6-azabicyclo[3.2.1]octane core **1.78**. The formal synthesis of this alkaloid was accomplished in 2000 by Woerpel and co-workers via a [3 + 2] allylic silane annulation.[46] Electrophilic attack of **1.73** by chlorosulfonyl isocyanate, antiperiplanar to the silyl group,[47] gave the zwitterionic intermediate **1.76** (**Scheme 20**).[48] A 1,2-silyl migration[49] occurred providing the more stable allylic cation **1.77**. Ring closure at C-1 of the allylic cation (route *a*) gave desired *N*-chlorosulfonyl bicyclic lactam, which was subsequently reduced to **1.74** using Na_2SO_3.. Ring closure at C-3 (route *b*) yielded the bicyclic lactam which was finally reduced to compound **1.75**.



Scheme 20.

Noteworthy is the synthesis of optically active 2,3-dihydropyrroles that can be applied to the total synthesis of natural products such as Manzamine A and Stephacidin B, two potent antitumoral[50] compounds isolated respectively from marine sponges of the genera *Haliclona* and *Pellina*[51] and a fungal culture.[52]

In 2008 Gong and co-workers[53] reported the first catalytic asymmetric cycloaddition reaction of α-substituted isocyanoesters **1.79** to nitroolefins **1.80** by using 20% mol alkaloid-derived base **1.81** in CH_2Cl_2 at 35°C to form highly functionalized 2,3-dihydropyrroles **1.82** with excellent enantioselectivities (up to >99% *ee*) (**Scheme 21**).

The chiral base promoted an asymmetric Michael addition of isocyanoester **1.79** to electron-deficient olefins, such as nitroolefins **1.80**, by activating the acidic α-carbon atom of **1.79**, to generate an intermediate which underwent intramolecular cyclization affording 2,3-dihydropyrroles after proton shift.

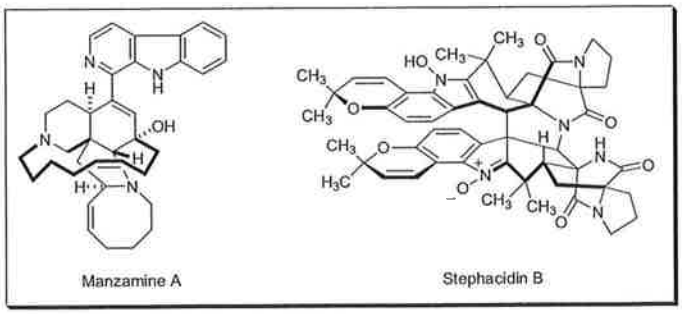
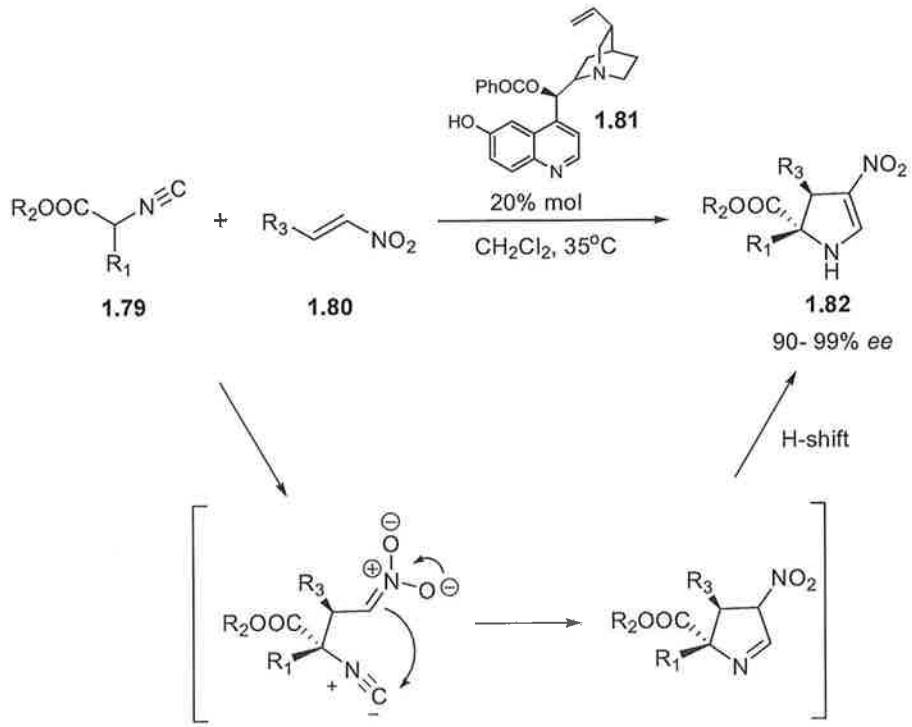


Figure 3.



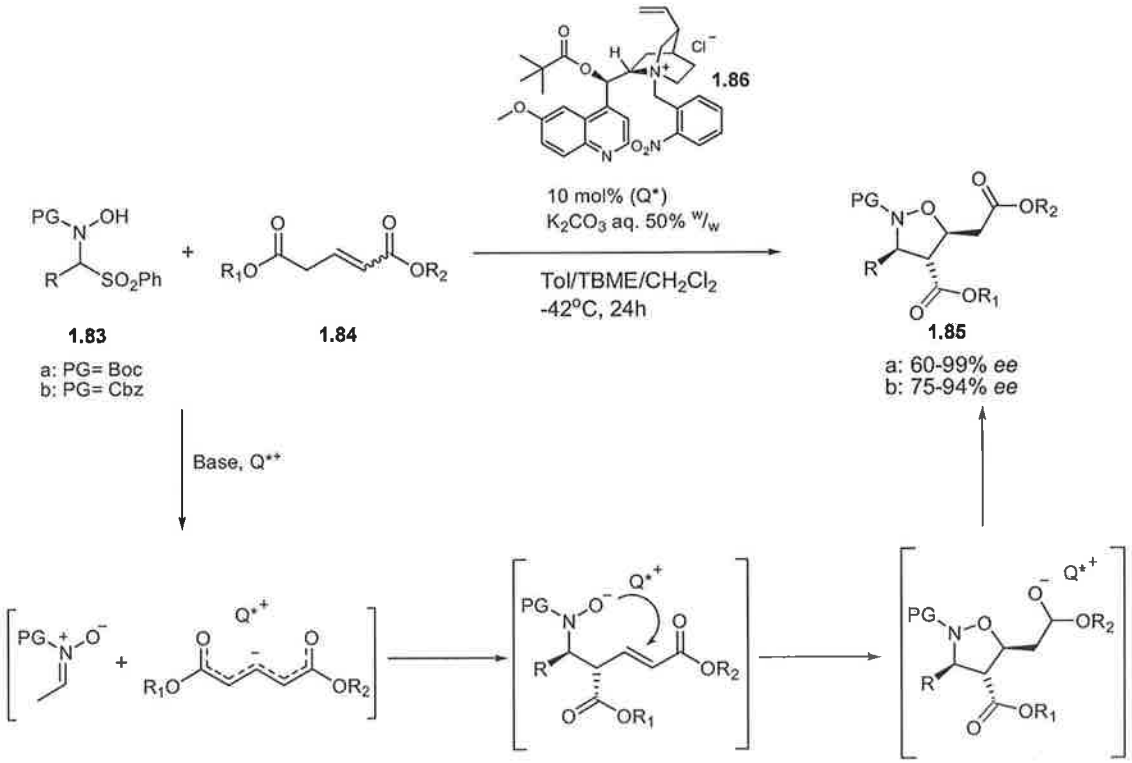
Scheme 21.

Another important catalytic [3 + 2] cycloaddition was developed in Ricci's laboratory in 2010.[54]

This reaction that involved *N*-Boc and *N*-Cbz-protected *N*-hydroxy-α-amido sulfones **1.83** as nitrone precursors and glutaconates **1.84** offers the possibility of generating isoxazolidines **1.85** (**Scheme 22**) with up to three new contiguous stereocenters, which

are precursors of broadly useful compounds such as 1,3-aminoalcohols, amino acids, azasugars and alkaloids.[55]

The reaction was performed using 10 mol% quinine-derived ammonium salt **1.86** in the presence of 5 equiv. of K_2CO_3 50% $^{w}/_{w}$ at -42°C in CH_2Cl_2 to generate compounds **1.85** in good yields and enantioselectivity comprised between 60 and 99% *ee*. The highly reactive *N*-carbamoyl nitrones could be formed *in situ* and undergo an enantioselective Mannich addition by the chiral quaternary ammonium enolate. The resulting anionic adducts should then directly cyclise intra-molecularly affording isoxazolidines **1.85**.



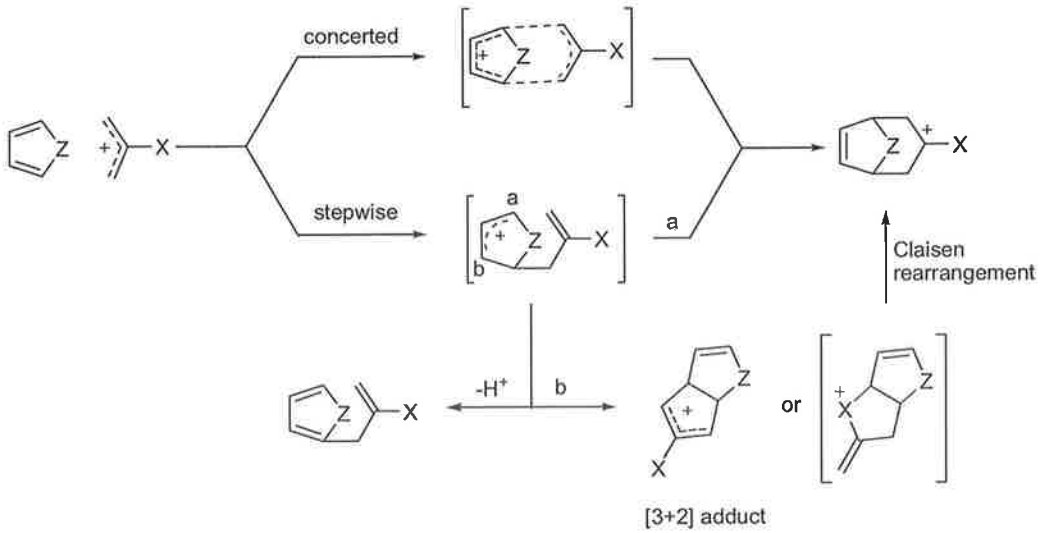
Scheme 22.

1.3 [4 + 3] Cycloaddition.

[4 + 3] Cycloadditions are important in the synthesis of seven-membered rings, more difficult to prepare than their smaller homologues due to a slight increase in entropy compared to six membered rings. This reaction can be considered as a [4π + 2π] involving an electron rich (4π electron, 4 carbon) diene and allylic cation (2π electron, 3 carbon) (**Scheme 23**).

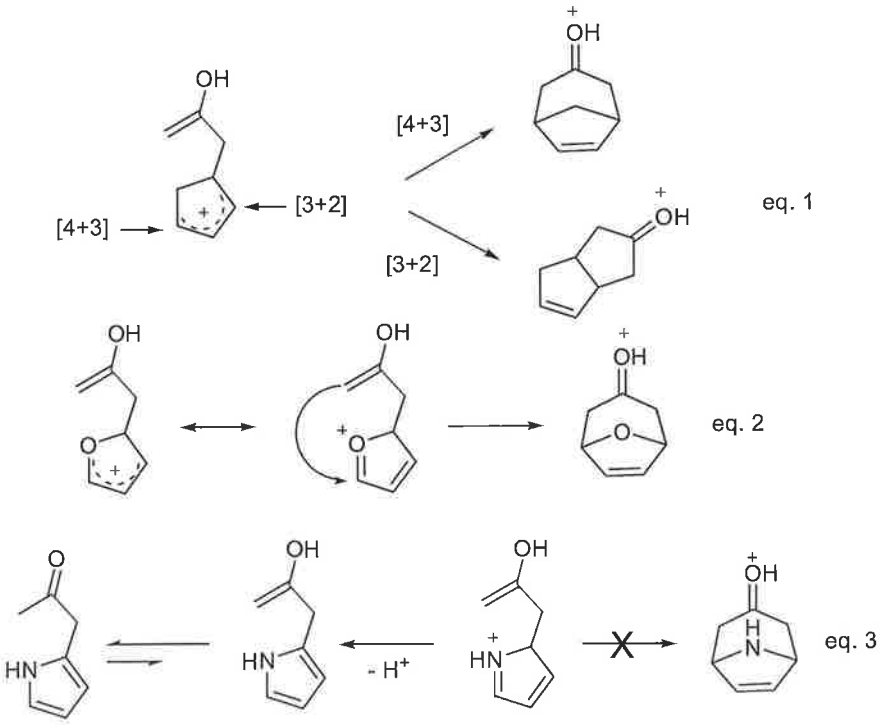
Scheme 23.

The mechanism of this reaction has been debated and two proposed pathways identified, namely a concerted pericyclic or a stepwise process (**Scheme 24**). The stepwise process involves the formation of an intermediate which could evolve to final adduct via pathway a or pathway b. The latter constitutes a formal [3 + 2] cycloaddition followed by a Claisen rearrangement.[56]



Scheme 24.

The nucleophilicity of the dienes employed is an important factor in these reactions. For instance, when 1,3-cyclopentadiene is used, the tandem [3 + 2] / Claisen process has some preference over the pericyclic [4 + 3] mechanism (**Scheme 25**, eq. 1); when furan is used, the pericyclic [4 + 3] cycloaddition is favored due to the stability of the intermediate (**Scheme 25**, eq. 2). Pyrroles are not good diene components in this chemistry and generate electrophilic substitution products rather than cycloadducts. This could be explained by the high stability of the 1-azabutadienyl cation, cyclization of which give the corresponding seven membered ring is energetically unfavorable (**Scheme 25**, eq. 3).[57]



Scheme 25.

The most useful dienophiles to date for use in this reaction are allyl cations substituted at the 2-position by an oxygen, termed oxyallyls (**Figure 3**).

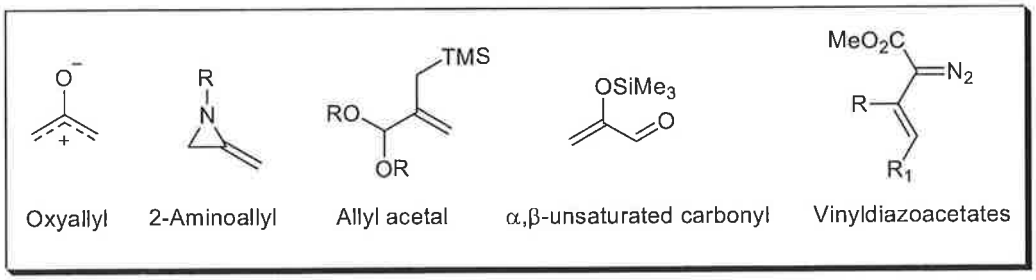


Figure 3.

This could be explained by the value of the LUMO of the oxyallyl cation, which is lower in energy and it can be lowered by increasing covalent character of O-M bond. Indeed, the reducing agent $Fe_2(CO)_9$ has found extensive use in the generation of oxyallyl cations, because of the highly covalent nature of the iron-oxygen bond, making this iron-oxo species one of the most electrophilic of its kind.

The electrophilicity of the oxyallyl cation influences the stereoselectivity of the [4 + 3] cycloaddition. By increasing the electrophilicity of the oxyallyl cation species, the selectivity decreases for the compact (boat-like) mode of reaction favoring the extended (chair-like) one (**Figure 4**).

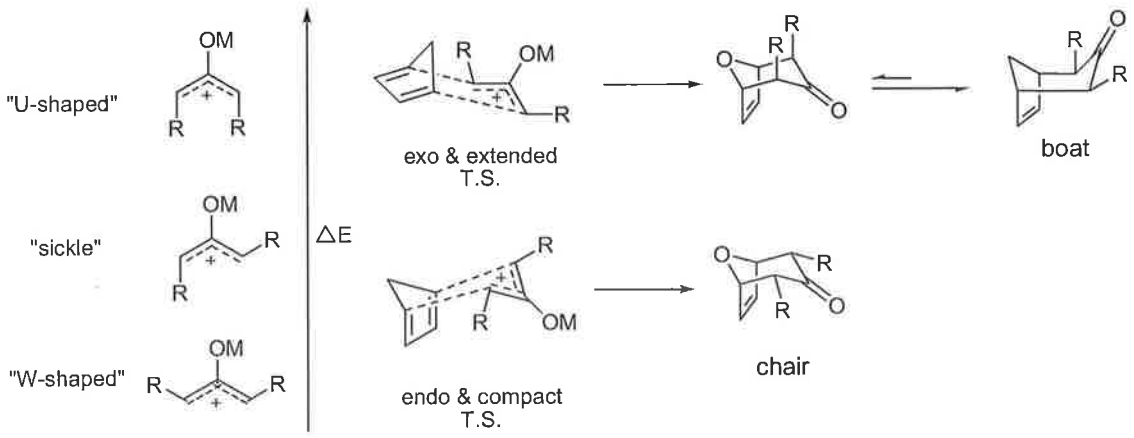


Figure 4.

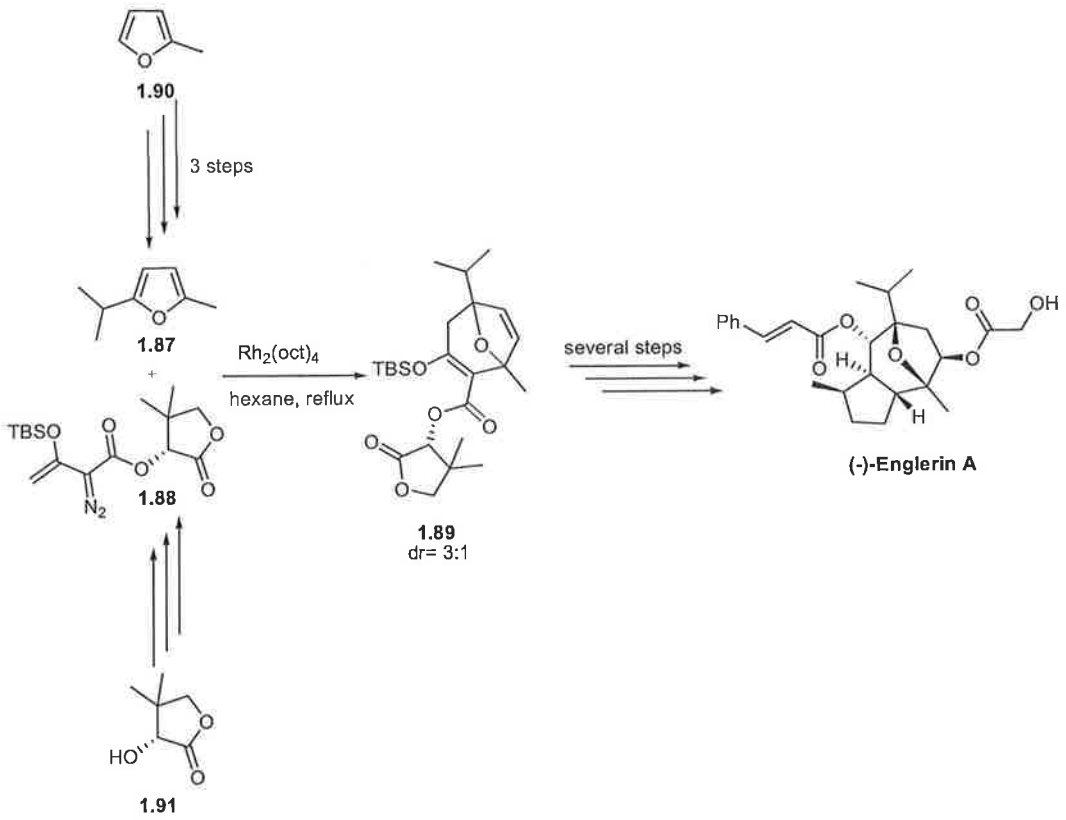
The oxyallyl species can adopt three different configurations. The "W" in the case of acyclic oxyallyls, the "U" form in cyclic species and the "sickle" form only in a few cases (**Figure 4**).

1.3.1 Metal-Catalyzed [4 + 3] Reactions: Rhodium and Palladium Catalyzed [4 + 3] Reactions.

Intermolecular and intramolecular cycloadditions catalyzed by transition-metal complexes are useful methods for convergent synthesis of cyclic materials.

Rh(II)-catalyzed [4 + 3] reactions have found important applications for the enantioselective and diastereoselective preparation of seven membered rings starting from diazo compounds. In 2010 Theodorakis and coworkers reported an enantioselective synthesis of (-)-Englerin A via a Rh-catalyzed [4 + 3] cycloaddition following an intramolecular aldol condensation.[58] (-)-Englerin A is a guaiane-type sesquiterpene that contains an uncommon oxygenated motif and has been isolated from the Tanzanian plant *Phyllanthus engleri*, remarkable in its highly potent and selective cytotoxicity against various renal cancer cell lines at low nanomolar level.[59]

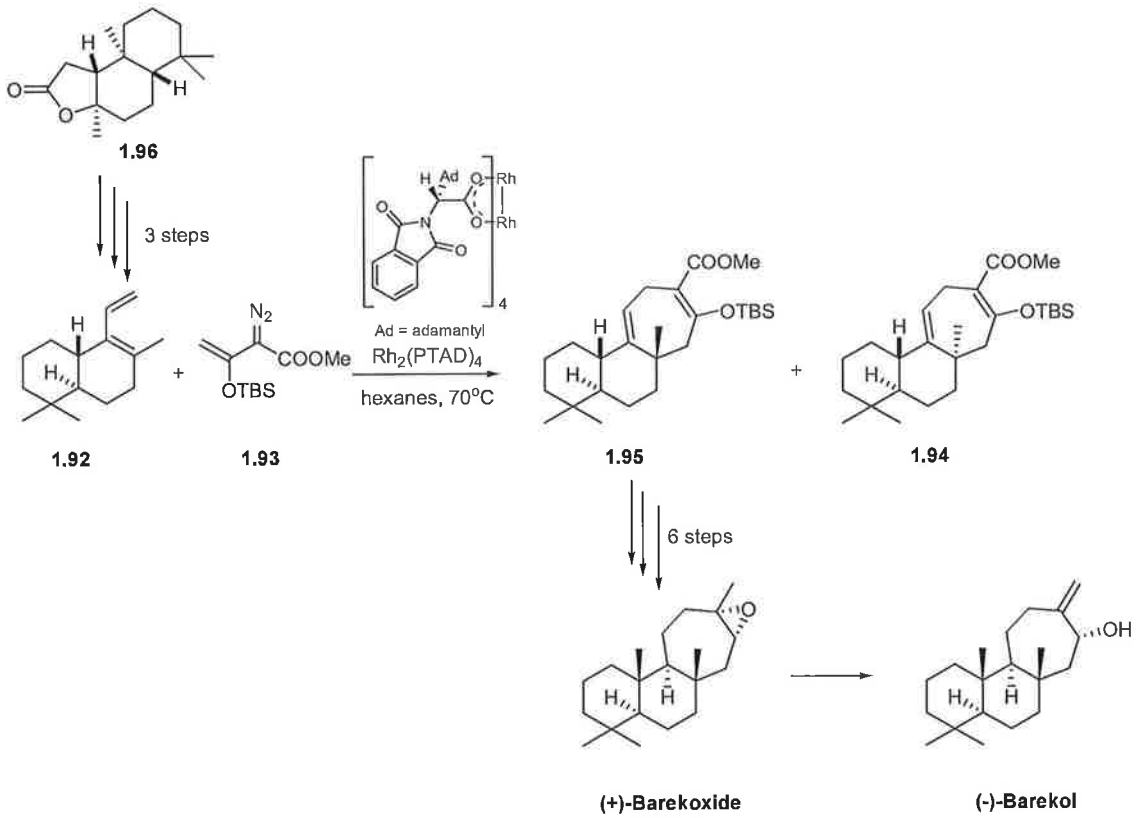
The reaction was performed between furan **1.87**, prepared in three steps from 2-methylfuran **1.90**,[60] and the chiral diazo ester **1.88,** which derived from (*R*)-pantolactone **1.91** in three steps.[61] The cycloaddition was catalyzed in the presence of 2 mol % of rhodium(II) octanoate in refluxing hexane giving the key oxatricyclic compound **1.89** in 90% yield (**Scheme 26**) with moderate diastereoselectivity (dr = 3 :1). (-)-Englerin A was synthesized in several steps from compound **1.89**.



Scheme 26.

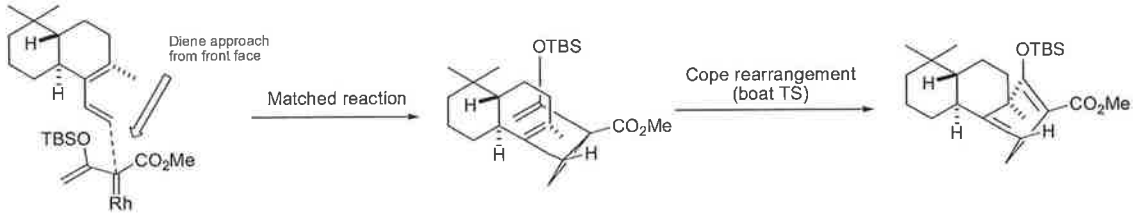
Sarpong's and Davies' groups applied a catalyst-controlled formal [4 + 3] cycloaddition[62] to the total synthesis of (+)-Barekoxide and (-)-Barekol, two terpenes isolated from the sponge *Chelonaplysilla erecta*, which have shown anti-HIV, antibiotic and antitumor activity.[63] The [4 + 3] cycloaddition was performed on diene **1.92**, prepared in three steps from commercially available scalerolide **1.96** and compound **1.93** in the presence of $Rh_2(PTAD)_4$ (**Scheme 27**). Due to the sterically crowed nature of the double bond in **1.92**, a temperature of 70°C and 3-5 equiv of **1.93** were required for an efficient reaction. When the reaction was conducted under the catalysis of Rh_2(*R*-PTAD)$_4$ (Tetrakis[(*S*)-(+)-(1-adamantyl)-(*N*-phthalimido)acetate]-dirhodium(II)) a 6 : 1 mixture of diastereomers was obtained in 65% yield in which **1.95** (47% yield) was predominant. On the contrary, the reaction carried out under the catalysis of Rh_2(*S*-PTAD)$_4$ gave a 9 : 1 mixture of diastereomers in 63% yield in which **1.94** was the major compound. In this manner, the

configuration of a demanding quaternary stereocenter at the B-C ring fusion was effectively controlled.



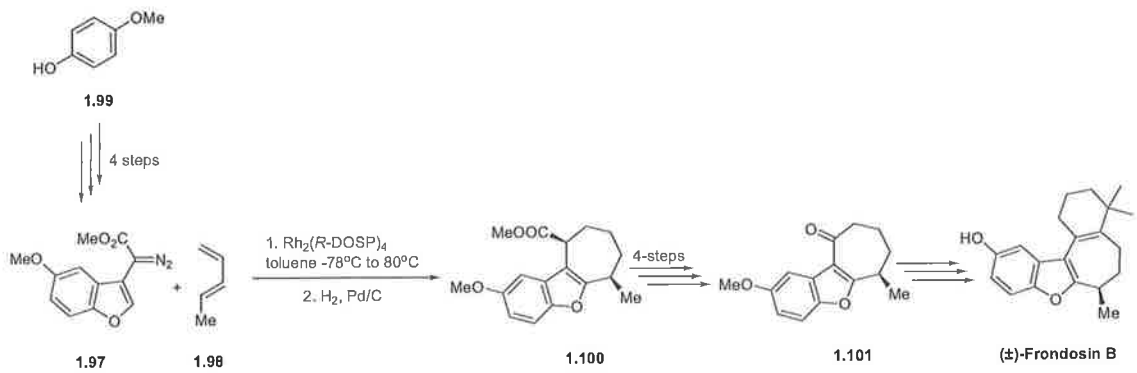
Scheme 27.

The stereochemistry of the [4 + 3] cycloaddition was controlled by the initial cyclopropanation, in which Rh_2(*R*-PTAD)$_4$ forced the diene to approach the dienophile from its front face. The synthesis of (+)-Barekoxide and (-)-Barekol from the tricycle **1.95** was readily achieved in six and seven steps respectively. Again, the stereochemistry of the [4 + 3] cycloaddition is controlled in the initial cyclopropanation. Theoretical calculations have shown that the alkene approaches in essentially an end-on mode, whereas the Cope rearrangement of the divinylcyclopropane proceeds through a boat transition state (**Scheme 28**).



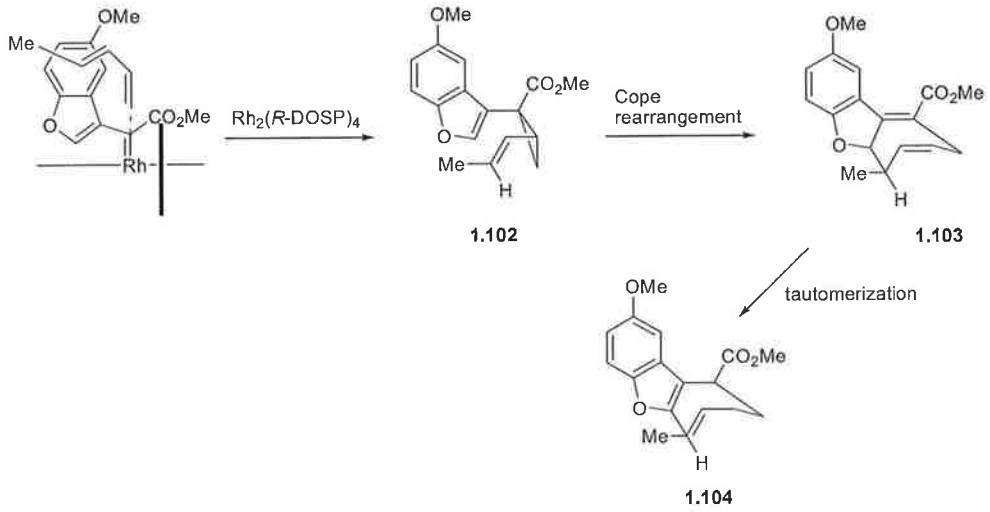
Scheme 28.

In 2008 Davies group reported an asymmetric [4 + 3] cycloaddition as a key step in the synthesis of (+)-Frondosin B.[64] Frondosin B, a member of a marine sesquiterpene family, was isolated by Freyer *et al.* from the marine sponge *Dysidea frondosa* in 1997. This compound has been found to be a micromolar inhibitor of interleukin-8 (IL-8) receptors and protein kinase C (PKC).[65] The application of the [4 + 3] cycloaddition to the formal synthesis of (+)-frondosin B would require the availability of methoxy derivative **1.97,** conveniently prepared from the commercially available 4-methoxyphenol **1.99,** as the carbenoid precursor. When the heteroaryldiazoacetate **1.97** was reacted with *trans*-piperylene **1.98** in the presence of Rh_2(*R*-DOSP)$_4$ (Tetrakis[(*R*)-(-)-*N*-(*p*-dodecylphenylsulfonyl)prolinato]-dirhodium) at 80°C, the mixture was completely converted to the desired [4 + 3] cycloadduct. Because this product rapidly decomposed, it was immediately subjected to hydrogenation to produce compound **1.100** in 57% yield, 97% *ee*, and >94% de (**Scheme 29**).



Scheme 29.

Compound **1.101** was synthetised in four steps from **1.100** which has been previously converted to frondosin B by Danishefsky.[66] The high enantioselectivity observed in the formation of the [4 + 3] cycloadducts was not surprising because it was well established that Rh_2(*R*-DOSP)$_4$ is capable of high enantioselection with a range of donor/acceptor-substituted carbenoids.[67] On the contrary, the high diastereoselectivity observed was surprising. The most reasonable mechanism to explain this reaction involves a diastereoselective cyclopropanation, followed by a Cope rearrangement and finally a stereoselective proton transfer (**Scheme 30**). The model for the Rh_2(*R*-DOSP)$_4$ cyclopropanation predicts the formation of the enantiomer **1.102** shown in **Scheme 30**.[68] The ring expansion of **1.102** via the Cope rearrangement to form **1.103** occurs through a boat transition state, and it proceeds with well-defined stereocontrol.[69] The novel step in this chemistry is the tautomerization of **1.103** to **1.104** to regenerate the benzofuran ring, which occurs without any observable scrambling.



Scheme 30.

Another rhodium-catalyzed [4 + 3] cycloaddition involved in a total synthesis was performed in Davies' laboratory in 2005.[70] They synthesized Vibsanin E, a member of a small family of diterpenes,[71] isolated from the Japanese fish poison plant *Viburnum awabuki* [72] in 1978. The first step of the synthesis was the Rh_2-(*S*-DOSP)$_4$[73] catalyzed [4

Chapter 2: Catalytic Asymmetric Conjugate Addition of Isocyanoacetates to 4-Nitro-5-styrylisoxazoles.

2.1 Introduction.

3-Methyl-4-Nitro-5-styrylisoxazoles **2.1** represent a class of poly-functional scaffold, which holds excellent potential for the generation of diversity.[1a-k]

Compound **2.1** can be readily prepared from commercially available 3,5-dimethyl-4-nitro-isoxazole and aromatic aldehydes (**Figure 1**).[2]

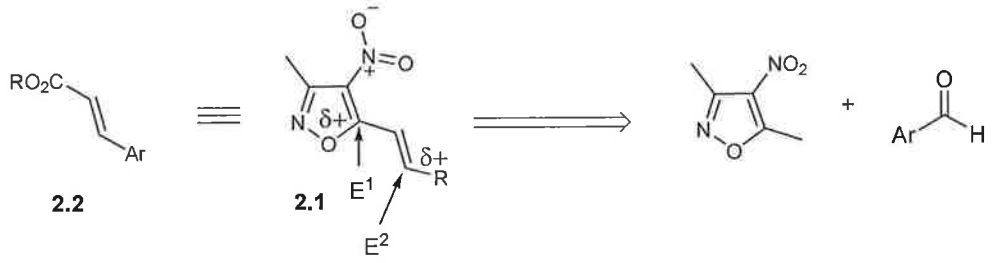
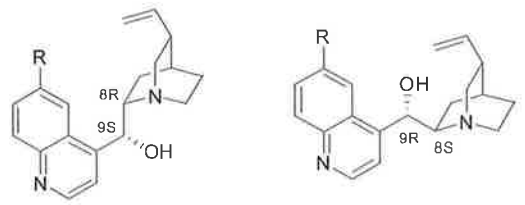


Figure 1.

Compounds **2.1** have two electrophilic centers that can be selectively reacted. Enolates, which are stabilized soft nucleophiles, react at the soft electrophilic center E^2, whereas hard nucleophiles such as hydroxide react exclusively at the hard electrophilic center E^1 (**Figure 1**). 4-Nitro-5-styrylisoxazoles **2.1**, that could be considered synthetic equivalent to cinnamates **2.2** but possessing an enhanced reactivity, emerged as optimal Michael acceptors in chiral settings employing chiral phase transfer catalysis.[3] Phase-transfer catalysis is a powerful method in organocatalysis based on ion pair interactions between a nucleophilic anion and a positively charged catalyst, often an ammonium salt. *Cinchona* alkaloids have been a popular natural source of organocatalysts due largely to their excellent commercial availability and low cost. Since the first *Cinchona* alkaloid-derived phase-transfer catalyst was disclosed in 1981, diverse generations of *Cinchona*-derived

phase-transfer catalysts have been developed and successfully applied to various asymmetric syntheses.

Cinchona is a genus of approximately 25 species in the family Rubiaceae, originally native to tropical South America. Since the introduction of *Cinchona* in the 16th century in Europe, their bark extracts have been employed as an herbal medicine to treat various diseases. As one major *Cinchona* alkaloid ingredient in the extract, quinine was used to treat fevers, especially malaria.[4] Depending on their pseudoenantiomeric stereo-structure and functional groups, four kinds of *Cinchona* alkaloid are known. As shown in **Figure 2**, *Cinchona* alkaloids have a quite unique structure involving a sterically hindered tertiary amino alcohol with various functional groups, such as the 9-hydroxy group, the 6-methoxy group on the quinoline ring, and the 10,11-vinyl group on the quinuclidine moiety. Their unique structure and commercial availability at low prices imbue them with many applications in organic chemistry, especially asymmetric synthesis, as an efficient organocatalyst or chiral ligand.[5]



Cinchonidine (R=H)
Quinine (R=OMe)

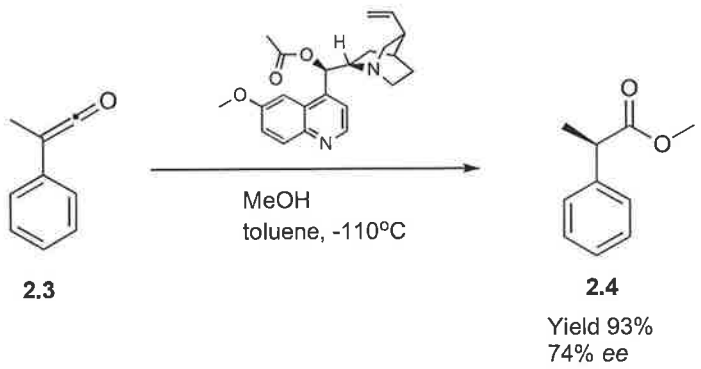
Cinchonine (R=H)
Quinidine (R=OMe)

Figure 2. Four kinds of *Cinchona* alkaloid that represent 50% of the total alkaloid profile.

In 1820 Pasteur used a quinine derivative for resolution of a racemic tartaric acid,[6] and for many years this remained the chiral resolving agent of choice.[7] From an historical perspective, the first example of asymmetric catalysis was reported in 1912 by Breding and Fiske who described the hydrocyanation of aldehydes to proceed in low enantioselectivity when quinine and quinidine were used as catalysts.[8]

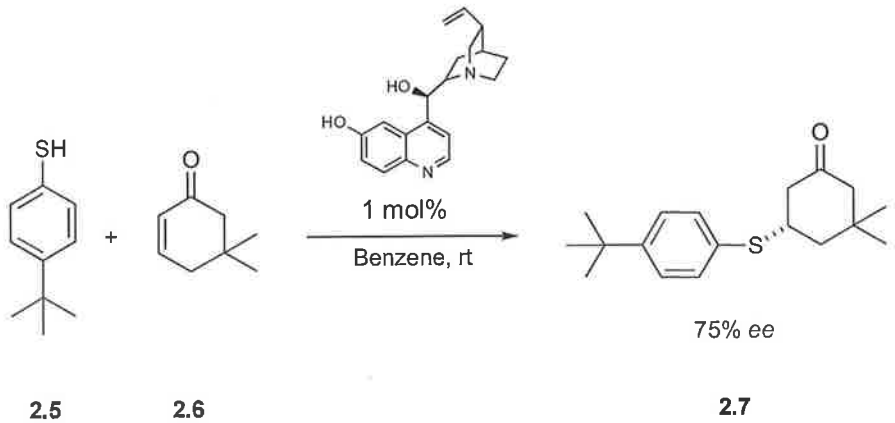
Another milestone in *Cinchona* catalysis was the use by Pracejus *et al.* of *O*-Acetyl quinine in the methanolysis of phenylmethylketene **2.3** to (–)-α-phenyl methylpropionate

2.4 which was obtained in 74 % *ee* (**Scheme 1**).[9]



Scheme 1.

A considerable improvement in *Cinchona* chiral catalysis was achieved in the 1970s. Wynberg, Hiemstra and co-workers studied several reactions catalyzed by quinine and its derivatives, obtaining excellent results and a quantity of mechanistic data for the addition of thiophenol **2.5** to cyclohexenone **2.6** to give compound **2.7** (**Scheme 2**).[10]

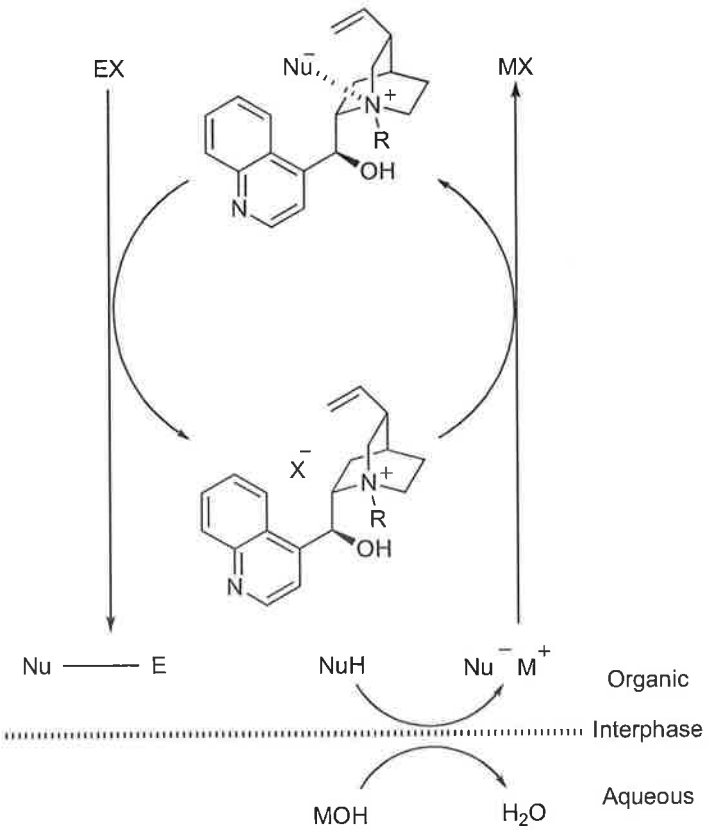


Scheme 2.

The first highly enantioselective reaction catalyzed by *Cinchona* alkaloids in an organic reaction was the asymmetric dihydroxylation of olefins as disclosed by the Sharpless group at the end of the 1970s.[11] They employed C(9)-*O*-substituted *Cinchona* alkaloids as

organoligands of OsO_4 for the oxidation of unsaturated substrates, affording chiral dihydroxy compounds. Further development of *Cinchona*-based dimeric catalysts enlarged the scope of the substrates and made the asymmetric dihydroxylation practical enough to be applied in industrial processes. The tertiary amine of the *Cinchona* alkaloids was derivatized by *N*(1)-alkylation to provide a variety of quaternary ammonium salts serving as efficient chiral phase-transfer catalysts (PTCs).

Since phase-transfer catalysis was introduced by Starks in the late 1960s,[12] it has been popularly applied in various organic reactions thus far, and is regarded as a practical synthetic methodology that requires simple operation, mild reaction conditions, it is inexpensive and enables environmentally friendly chemical reactions, and is facile to adapt to the large scale of industrial processes. Although the exact mechanism of the phase-transfer catalysis remains elusive, one of the representative mechanisms is shown in **Scheme 3**.

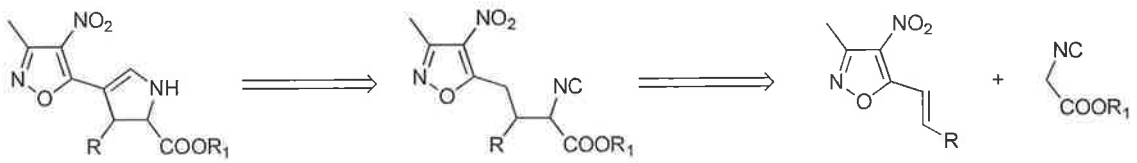


Scheme 3. Representative mechanism of phase-transfer catalysis (PTC).

The quaternary ammonium cation forms a nucleophilic ionic complex with an anion of the nucleophile, such as an active methylene compound, generated by deprotonation with an alkali inorganic base at the interphase of the organic and aqueous phases. The nucleophilic ionic complex, $R_4N^+Nu^-$, then reacts with the electrophile, such as an alkyl halide, unsaturated enone, imine, aldehyde or ketone, to provide the resulting products, Nu–E. Finally, the quaternary ammonium salt returns back to the interface initiating a new cycle. During the sequential pathway of a catalytic phase-transfer reaction, the *Cinchona*-derived quaternary ammonium salt generates a chiral environment in the stage of the nucleophilic ionic complex, N^+Nu^-, of which the least sterically hindered face is approached by the electrophile to afford the chiral product. In the past few decades, numerous chiral phase-transfer catalysts have been developed and successfully applied to various asymmetric syntheses.[13]

2.2 Aim.

As part of our programme of research devoted to the application of scaffold **2.1** as synthetic equivalent of cinnamate esters we considered the preparation of compound **2.10**, starting from cyclization of isocyanides **2.9**, which in turn could be obtained from a Michael addition between styrylisoxazoles **2.1** and isocyanoacetates **2.8** (**Scheme 4**).



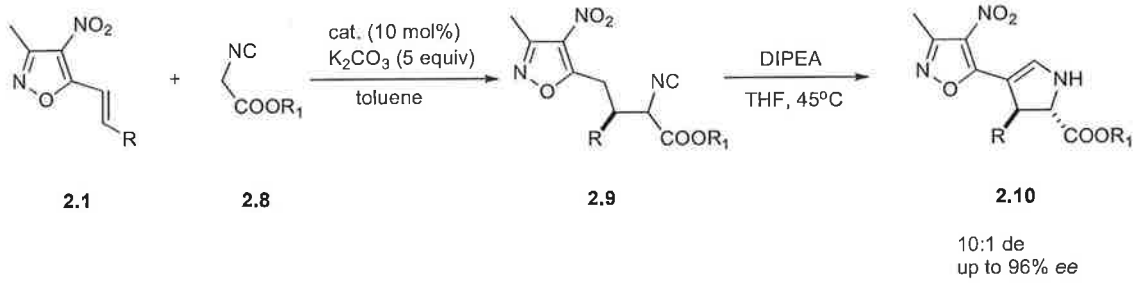
2.10 **2.9** **2.1** **2.8**

Scheme 4.

Compound **2.10** holds the pyrrolidine structure and could be considered as unnatural non proteinogenic aminoacids.

2.3 Results and Discussion.

Herein we present an extension of this study in which title compounds **2.1** were used for the development of a new organocatalytic [3 + 2] cycloaddition reaction. Hence compounds **2.1** were reacted with isocyanide esters **2.8** in the presence of a chiral phase transfer catalyst to obtain desired Michael adducts **2.9** in high yield and 86-96% *ee*. Compounds **2.9** were subsequently converted to dihydropyrrolidines **2.10** by reaction of an organic base such as DIPEA (**Scheme 5**).



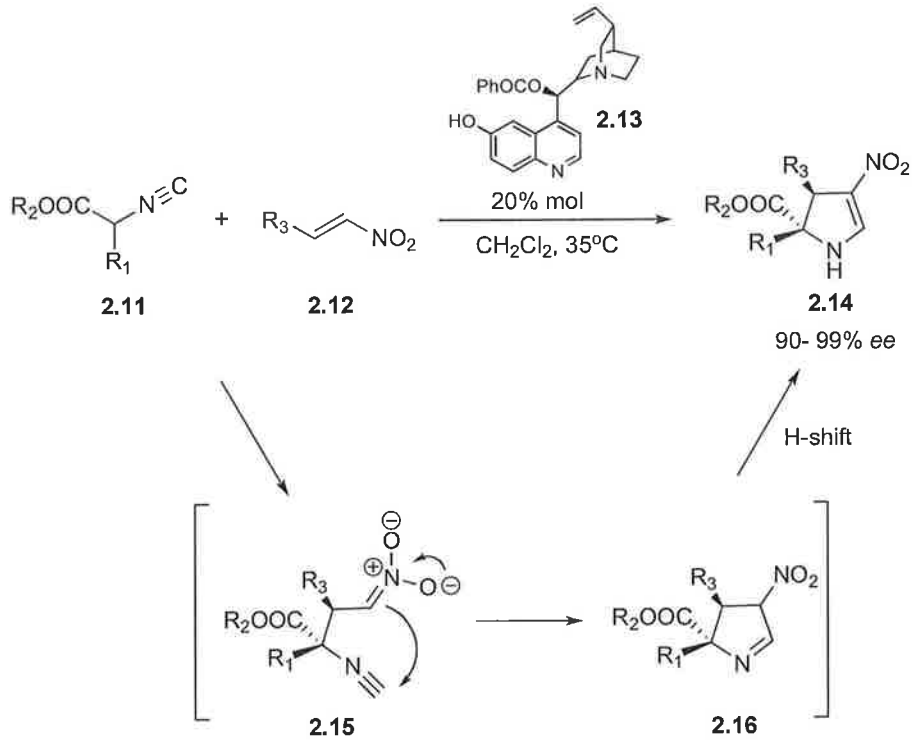
2.1 **2.8** **2.9** **2.10**

10:1 de
up to 96% *ee*

Scheme 5.

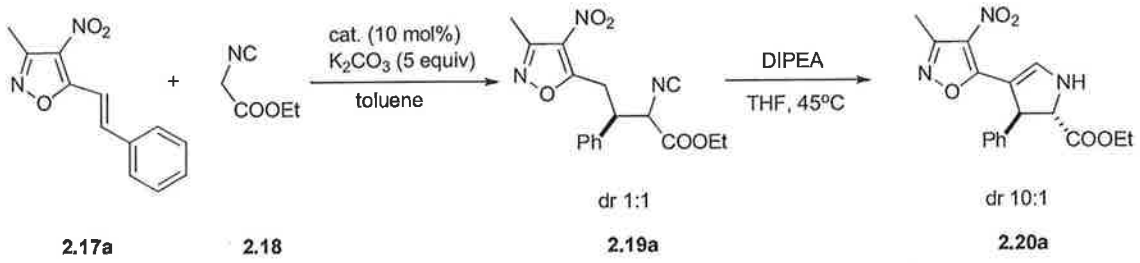
This work was inspired by Gong et al. who developed an highly enantioselective addition of isocyanoesters **2.11** to nitroolefins **2.12** (**Scheme 6**) using a *Cinchona* alkaloid **2.13** (**Figure 1**) as a chiral catalyst.[14] Despite the high yields and enantioselectivity obtained, the method described in **Scheme 6** worked only with 2-substituted isocyanoesters **2.11** ($R_1 \neq H$) and failed to work when unsubstituted isocyanoesters such as **2.8** was employed. While on one side this method gave precious quaternary aminoacids, on the other the presence of a quaternary stereocentre may pose limitation to the use of adducts **2.14** for the preparation of certain natural alkaloids. Additionally, due to the hard nucleophilicity of the resulting anion in **2.15**, the reaction between **2.11** and **2.12** could not be stopped but proceeded to dihydropyrrolidines **2.14**. We have explained this as a consequence of the high nucleophilicity of the aci-nitro nucleophile in **2.15** which readily reacted with the isocyanide electrophile to give the cyclised compound. Considering the importance of isocyanides in multicomponent (MRC) reactions, *e.g.* Ugi or Passerini reactions, and in

general for the preparation of peptidomimetic scaffolds, a process allowing stopping of the reaction and retaining the isonitrile would be desirable.

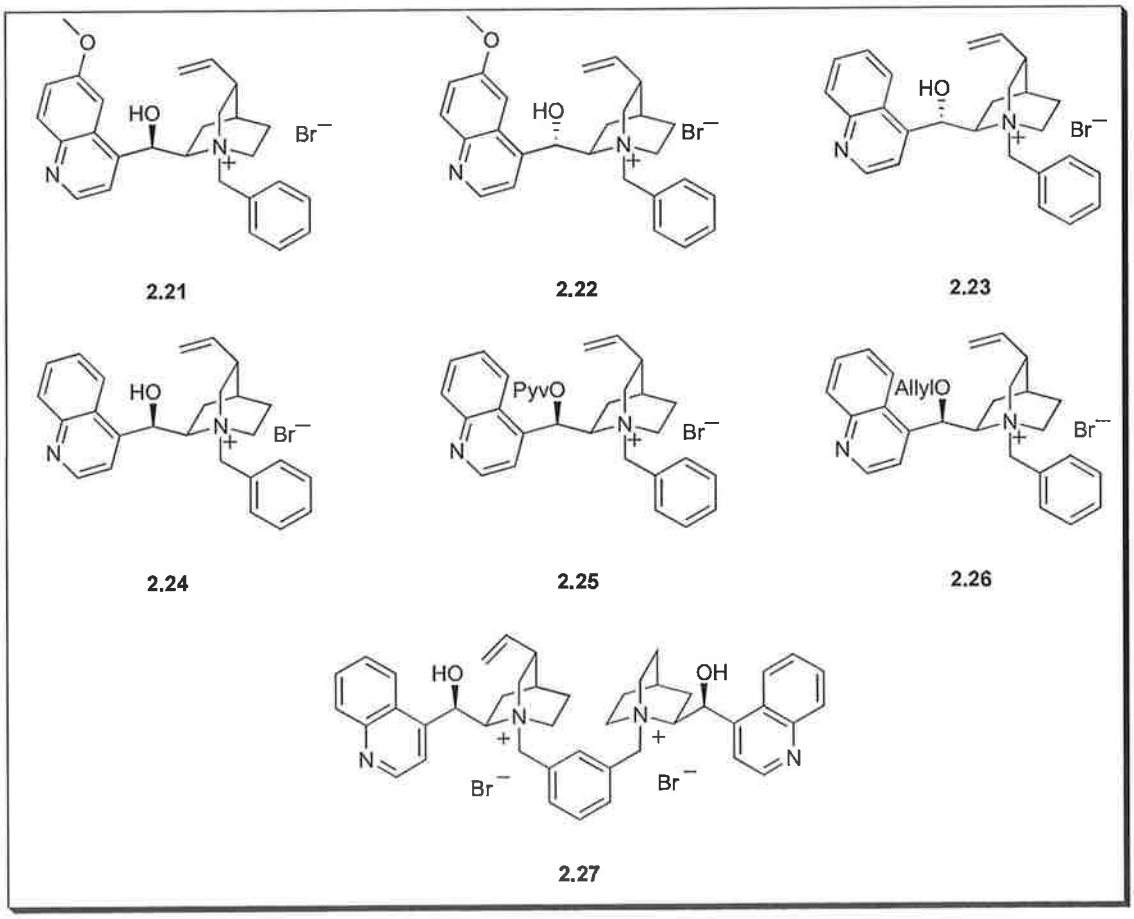


Scheme 6.

We started our investigation by using phase-transfer conditions for the preparation of **2.19** (**Scheme 7**). For this purpose, 1.0 mmol of 3-methyl-4-nitro-5-styryl-isoxazole **2.17** and 3 mmol of ethylisocyanoacetate **2.18** were reacted in the presence of 10 mol% of several *Cinchona*-derived quaternary ammonium salts and 2 equiv. of suitable inorganic bases in toluene at different temperatures (**Table 1**). Compound **2.19** was obtained as an inseparable mixture of two diastereoisomers (dr 1:1). Due to the impossibility of getting a good separation of the four enantiomers by chiral stationary HPLC, **2.19** was converted to compound **2.20a** using DIPEA in THF at 45°C. The cyclic product was obtained as mixture of 2 diastereoisomers (dr 10:1) easily separated by chromatography on silica gel.



Scheme 7.



Entry	Cat.	Base	T (°C)	Solvent	h	Conv.[b]	*ee* (%)[c]
1	**2.21**	K_3PO_4 50% $^{w}/_{w}$	r.t.	Tol.	15	0%	-
2	**2.21**	K_3PO_4	r.t.	Tol.	15	98%	22
3	**2.21**	Cs_2CO_3 66% $^{w}/_{w}$	r.t.	Tol.	15	0%	15
4	**2.21**	Cs_2CO_3	r.t.	Tol.	15	96%	45
5	**2.21**	K_2CO_3 50% $^{w}/_{w}$	r.t.	Tol.	15	0%	33
6	**2.21**	K_2CO_3	r.t.	Tol.	15	96%	41

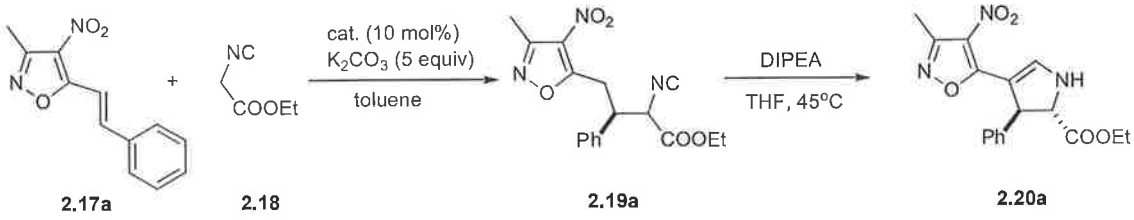
7	**2.21**	NaOH 30% $^{w}/_{w}$	r.t.	Tol.	15	0%	-
8	**2.21**	KOH 30% $^{w}/_{w}$	r.t.	Tol.	15	0%	-
9	**2.21**	K_2CO_3	-20	Tol.	15	50%	50
10	**2.21**	Cs_2CO_3	-20	Tol.	15	50%	50
11	**2.21**	Cs_2CO_3	0	Tol.	15	96%	20
12	**2.21**	Cs_2CO_3	-35	Tol.	15	50%	60
13	**2.21**	Cs_2CO_3	-42	Tol.	15	40%	55
14	**2.21**	KOH	-42	Tol.	15	0%	-
15	**2.21**	NaOH	-42	Tol.	15	0%	-
16	**2.21**	NaOH	-60	Tol.	15	0%	-
17	**2.21**	KOH	-60	Tol.	15	8%	-
18	**2.21**	K_2CO_3 50% $^{w}/_{w}$	-10	Tol.	15	27%	24
19	**2.21**	K_2CO_3	-10	Tol.	15	45%	42
20	**2.21**	K_2CO_3	-10	Tol.	15	48%	45
21	**2.21**	K_3PO_4	-10	Tol.	15	32%	30
22	**2.21**	K_2CO_3 50% $^{w}/_{w}$	-20	Tol.	63	48%	52
23	**2.21**	K_2CO_3	-20	Tol.	63	38%	58
24	**2.21**	Cs_2CO_3 66% $^{w}/_{w}$	-20	Tol.	63	61%	22
25	**2.21**	Cs_2CO_3	-20	Tol.	63	85%	55
26	**2.21**	K_3PO_4	-20	Tol.	63	32%	52
27	**2.21**	K_3PO_4 50% $^{w}/_{w}$	-20	Tol.	63	29%	43
28	**2.21**	K_2CO_3 50% $^{w}/_{w}$	-40	Tol.	63	21%	30
29	**2.21**	K_2CO_3	-40	Tol.	63	0%	-
30	**2.21**	Cs_2CO_3 66% $^{w}/_{w}$	-40	Tol.	63	25%	22
31	**2.21**	Cs_2CO_3	-40	Tol.	63	38%	23
32	**2.21**	K_3PO_4	-40	Tol.	63	0%	-
33	**2.21**	K_3PO_4 50% $^{w}/_{w}$	-40	Tol.	63	11%	14
34	**2.22**	K_2CO_3 50% $^{w}/_{w}$	-20	Tol.	63	60%	55
35	**2.22**	Cs_2CO_3	-20	Tol.	63	51%	50
36	**2.23**	K_2CO_3 50% $^{w}/_{w}$	-20	Tol.	63	25%	21
37	**2.23**	Cs_2CO_3	-20	Tol.	63	79%	38
38	**2.24**	KOH	-42	Tol.	15	0%	-
39	**2.24**	Cs_2CO_3	-42	Tol.	15	40%	50
40	**2.24**	NaOH	-42	Tol.	15	0%	-
41	**2.24**	Cs_2CO_3	-20	Tol.	15	50%	9
42	**2.24**	Cs_2CO_3	-20	Tol:DCM (9:1)	15	0% [a]	-
43	**2.24**	Cs_2CO_3	-20	Tol:DIPE (9:1)	15	50%	60
44	**2.24**	Cs_2CO_3	-20	Xylene	15	50%	62
45	**2.24**	Cs_2CO_3	-20	DIPE	15	0%	-
46	**2.24**	Cs_2CO_3	-60	Tol.	15	0%	-
47	**2.24**	CsOH	-60	Tol.	15	5%	-
48	**2.24**	CsOH	-42	Tol.	15	0%	-
49	**2.24**	K_2CO_3 50% $^{w}/_{w}$	-20	Tol.	63	73%	71
50	**2.24**	Cs_2CO_3	-20	Tol.	63	80%	**75**

51	**2.25**	Cs_2CO_3	-20	Tol.	15	23%	0
52	**2.26**	Cs_2CO_3	-20	Tol.	15	23%	0
53	**2.27**	Cs_2CO_3	-20	Tol.	63	44%	49

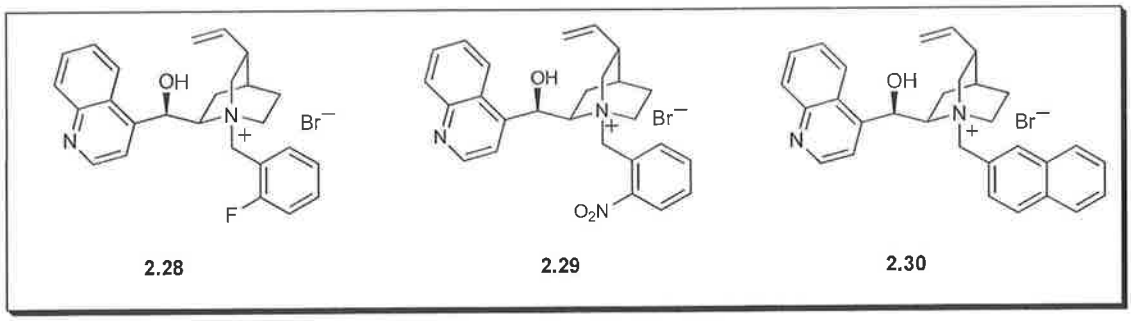
[a] Conditions: Styrylisoxazole **2.17** (0.1 mmol), ethylisocyanoacetate **2.18** (0.2 mmol), cat. (0.01 mmol), toluene (1 mL). [b] Determined by ^{1}H-NMR of the crude mixture. [c] Determined by chiral stationary HPLC on the major diastereisomer of compound **2.20a**.

Table 1. Results from the screening of *Cinchona* derived catalysts **2.21-2.27**.[a]

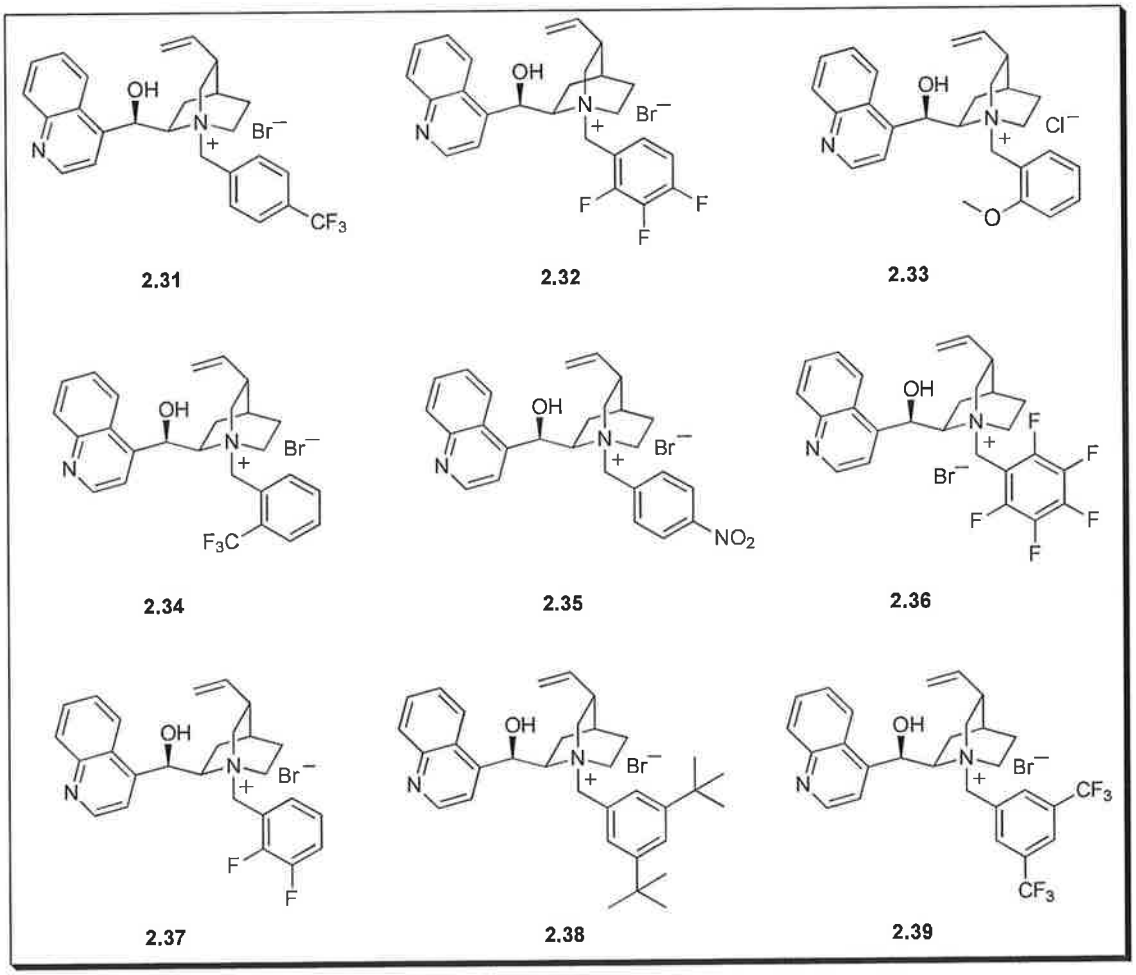
These experiments exposed the conditions as satisfactory from an asymmetric standpoint: the Cinchona derived catalyst afforded the desired product with general high conversion and promising enantiomeric excess, up to a maximum of 75%. The higher enantiomeric excess was obtained at -20°C using *N*-benzyl cinchonidinium bromide **2.24** (**Table 1**, entry 50) as the catalyst and Cs_2CO_3 as base. The second generation catalyst *O*-allyl-*N*-benzylcinchonidinium (**Table 1**, entry 51) bromide **2.26** and *O*-pivaloyl-*N*-benzylcinchonidinium bromide **2.25** (**Table 1**, entry 52) gave low conversion and no enantiomeric excess. The third generation catalyst **2.27** gave only 44% conversion and 49% of enantiomeric excess (**Table 1**, entry 53). Clearly, based on these results, the OH played a crucial effect in the enantiodetermining step. Based on results collected (**Table 1**) on the *N*-benzylcinchonidinium bromide catalyst, a series of *N*-benzylcinchonidinium salts **2.28-2.39** were prepared from cinchonidine and benzyl bromides containing various functional groups (**Table 2**).



2.17a **2.18** **2.19a** **2.20a**



2.28 **2.29** **2.30**



Entry	Cat.	Base	T(°C)	Solvent	t(h)	Conv.[a]	*ee* (%)[b]
1	**2.28**	KOH	-10	Tol.	15	99%	77
2	**2.28**	K_3PO_4 50% $^{w}/_{w}$	-10	Tol.	15	75%	66
3	**2.28**	CsOH	-10	Tol.	15	0%	-
4	**2.28**	Cs_2CO_3	-10	Tol.	15	58%	54
5	**2.28**	K_2CO_3 50% $^{w}/_{w}$	-10	Tol.	15	16%	25
6	**2.28**	CsOH	-20	Tol.	15	40%	73
7	**2.28**	CsOH	-20	Xylene	15	9%	50
8	**2.28**	Cs_2CO_3 66% $^{w}/_{w}$	-20	Tol.	15	71%	21
9	**2.28**	K_2CO_3 50% $^{w}/_{w}$	-20	Tol.	15	40%	70
10	**2.28**	NaOH	-20	Tol.	15	0%	-
11	**2.28**	K_3PO_4	-20	Tol.	15	8%	18
12	**2.28**	K_2CO_3	-20	Tol.	15	0%	-
13	**2.28**	NaOH 30% $^{w}/_{w}$	-20	Tol.	15	19%	54
14	**2.28**	KOH 30% $^{w}/_{w}$	-20	Tol.	15	0%	-
15	**2.28**	KOH	-20	Tol.	15	33%	78
16	**2.28**	KOH	-20	Tol.:DCM (9:1)	15	93%	72[c]

17	**2.28**	KOH	-20	Xylene	15	40%	53[c]
18	**2.28**	K_3PO_4 50% $^{w}/_{w}$	-20	Tol.:DCM (9:1)	15	53%	22[c]
19	**2.28**	K_3PO_4 50% $^{w}/_{w}$	-20	Tol.	15	70%	76
20	**2.28**	K_3PO_4 50% $^{w}/_{w}$	-20	Xylene	15	32%	54
21	**2.28**	Cs_2CO_3	-20	Tol.	63	87%	79
22	**2.28**	KOH	-30	Tol.	15	87%	74[c]
23	**2.28**	K_3PO_4 50% $^{w}/_{w}$	-30	Tol.	15	36%	74
24	**2.28**	CsOH	-42	Tol.	15	0%	-
25	**2.28**	CsOH	-42	Tol.	15	95%	34[d]
26	**2.28**	KOH	-42	Tol.	15	70%	55[d]
27	**2.28**	KOH	-60	Tol.	15	71%	58[d]
28	**2.28**	CsOH	-60	Tol.	15	89%	43[d]
29	**2.29**	CsOH	-20	Tol.	15	44%	55
30	**2.29**	K_2CO_3	-20	Tol.	15	45%	62
32	**2.29**	NaOH	-20	Tol.	15	27%	16
33	**2.29**	KOH	-20	Tol.	15	60%	55
34	**2.29**	K_3PO_4	-20	Tol.	15	32%	15
35	**2.29**	Cs_2CO_3	-20	Tol.	63	85%	56
36	**2.29**	Cs_2CO_3 66% $^{w}/_{w}$	-20	Tol.	15	67%	12
37	**2.29**	K_2CO_3 50% $^{w}/_{w}$	-20	Tol.	15	0%	-
38	**2.29**	NaOH 30% $^{w}/_{w}$	-20	Tol.	15	42%	8
39	**2.29**	KOH 30% $^{w}/_{w}$	-20	Tol.	15	0%	-
40	**2.29**	K_3PO_4 50% $^{w}/_{w}$	-20	Tol.	15	0%	-
41	**2.30**	Cs_2CO_3	-20	Tol.	63	87%	49
42	**2.30**	K_3PO_4 50% $^{w}/_{w}$	-20	Tol.	15	49%	34[c]
43	**2.30**	KOH	-20	Tol.	15	35%	32[c]
44	**2.30**	CsOH	-20	Tol.	15	46%	68
45	**2.30**	CsOH	-42	Tol.	15	55%	7
46	**2.30**	CsOH	-60	Tol.	15	68%	5
47	**2.31**	Cs_2CO_3	0	Tol.	15	78%	80[e]
48	**2.31**	Cs_2CO_3	-20	Tol.	63	84%	86
49	**2.31**	Cs_2CO_3	-20	Tol:DCM (7:3)	63	70%	80
50	**2.31**	Cs_2CO_3	-20	Tol:TBME (7:3)	63	73%	83
51	**2.31**	K_3PO_4	-20	Tol.	63	73%	80
52	**2.31**	K_2CO_3	-20	Tol.	63	36%	85
53	**2.31**	K_3PO_4 50% $^{w}/_{w}$	-20	Tol.	40	89%	86
54	**2.31**	Cs_2CO_3 66% $^{w}/_{w}$	-20	Tol.	64	76%	74
55	**2.31**	K_2CO_3 50% $^{w}/_{w}$	-20	Tol.	64	83%	84
56	**2.31**	Cs_2CO_3	-35	Tol.	65	62%	80
57	**2.31**	K_3PO_4	-35	Tol.	65	20%	-
58	**2.31**	K_2CO_3	-35	Tol.	65	55%	81
59	**2.31**	Cs_2CO_3 66% $^{w}/_{w}$	-35	Tol.	65	86%	66
60	**2.31**	K_3PO_4 50% $^{w}/_{w}$	-35	Tol.	65	88%	87
61	**2.31**	K_2CO_3 50% $^{w}/_{w}$	-35	Tol.	65	56%	81
62	**2.31**	Cs_2CO_3	-45	Tol.	168	77%	78

63	**2.31**	K_2CO_3	-45	Tol.	168	22%	78
64	**2.31**	Cs_2CO_3 66% $^{w}/_{w}$	-45	Tol.	168	21%	17
65	**2.31**	K_3PO_4 50% $^{w}/_{w}$	-45	Tol.	168	7%	-
66	**2.31**	K_2CO_3 50% $^{w}/_{w}$	-45	Tol.	168	0%	-
67	**2.31**	NaOH	-78	Tol.	168	12%	62
68	**2.31**	KOH	-78	Tol.	168	17%	47
69	**2.31**	CsOH	-78	Tol.	168	32%	82
70	**2.31**	NaOH 30% $^{w}/_{w}$	-78	Tol.	168	21%	86
71	**2.32**	K_2CO_3	0	Tol.	13	78%	77
72	**2.32**	K_2CO_3	0	Tol.	13	78%	80[e]
73	**2.32**	K_2CO_3	-10	Tol.	24	74%	83
74	**2.32**	Cs_2CO_3	-20	Tol.	63	84%	86
76	**2.32**	Cs_2CO_3	-20	Tol.	138	85%	85[f]
77	**2.32**	Cs_2CO_3	-20	Tol:DCM (7:3)	64	89%	80
78	**2.32**	Cs_2CO_3	-20	Tol:TBME (7:3)	64	85%	80
79	**2.32**	Cs_2CO_3 66% $^{w}/_{w}$	-20	Tol.	64	50%	10
80	**2.32**	K_2CO_3 50% $^{w}/_{w}$	-20	Tol.	64	52%	89
81	**2.32**	K_3PO_4	-20	Tol.	111	58%	85
82	**2.32**	K_3PO_4 50% $^{w}/_{w}$	-20	Tol.	111	91%	85
83	**2.32**	K_2CO_3	-20	Tol.	111	85%	91
84	**2.32**	K_2CO_3	-20	Tol.	64	87%	86[g]
85	**2.32**	K_2CO_3	-20	Tol.	40	84%	85[h]
86	**2.32**	K_2CO_3	-20	Tol.	17	32%	71[i]
87	**2.32**	K_2CO_3	-20	Tol.	40	70%	84[e]
88	**2.32**	K_2CO_3	-20	Tol: DCM (9:1)	40	69%	83[e,j]
89	**2.32**	K_2CO_3	-20	Tol:TBME (9:1)	40	66%	82[e,j]
90	**2.32**	K_2CO_3	-20	Xylene	40	72%	88
91	**2.32**	K_2CO_3	-20	TBME	40	35%	49
92	**2.32**	K_2CO_3	-20	DIPE	40	17%	58
93	**2.32**	K_2CO_3	-20	DCM	40	59%	59
94	**2.32**	CsF	-20	Tol.	43	17%	22
95	**2.32**	Li_2CO_3	-20	Tol.	43	0%	-
96	**2.32**	LiOH	-20	Tol.	43	16%	58
97	**2.32**	Cs_2CO_3	-35	Tol.	65	69%	79
98	**2.32**	K_3PO_4	-35	Tol.	65	24%	74
99	**2.32**	K_2CO_3	-35	Tol.	65	20%	76
100	**2.32**	Cs_2CO_3 66% $^{w}/_{w}$	-35	Tol.	65	29%	5
101	**2.32**	K_3PO_4 50% $^{w}/_{w}$	-35	Tol.	65	26%	79
102	**2.32**	K_2CO_3 50% $^{w}/_{w}$	-35	Tol.	65	11%	48
103	**2.32**	Cs_2CO_3.	-45	Tol.	168	67%	86
104	**2.32**	NaOH	-78	Tol.	168	6%	24
105	**2.32**	KOH	-78	Tol.	168	67%	82
106	**2.32**	CsOH	-78	Tol.	168	55%	28
107	**2.32**	NaOH 30% $^{w}/_{w}$	-78	Tol.	168	12%	60
108	**2.33**	Cs_2CO_3.	-20	Tol.	63	80%	60

109	**2.34**	Cs_2CO_3.	-20	Tol.	63	70%	43
110	**2.34**	Cs_2CO_3.	-20	Tol:TBME:DCM (3.5:3.5:3)	63	65%	34
111	**2.35**	Cs_2CO_3	-20	Tol.	63	75%	60
112	**2.36**	K_2CO_3	-20	Tol.	15	23%	68
113	**2.37**	K_2CO_3	-20	Tol.	15	39%	76
114	**2.38**	K_2CO_3	-20	Tol.	24	39%	81
115	**2.39**	K_2CO_3	-20	Tol.	15	51%	93
116	**2.39**	K_2CO_3	-20	Tol.	15	65%	96[k]
117	**2.39**	Cs_2CO_3	-20	Tol.	24	56%	78
118	**2.39**	K_3PO_4	-20	Tol.	24	75%	86
119	**2.39**	Na_2CO_3	-20	Tol.	24	-	-
120	**2.39**	CsOH	-20	Tol.	15	78%	93
121	**2.39**	Cs_2CO_3 66% $^w/_w$	-20	Tol.	24	41%	35
122	**2.39**	K_2CO_3 50% $^w/_w$	-20	Tol.	24	53%	84
123	**2.39**	K_3PO_4 50% $^w/_w$	-20	Tol.	24	76%	86
124	**2.39**	K_2CO_3	-20	Tol.	24	35%	86[l]
125	**2.39**	CsOH	-20	Tol.	24	68%	94
126	**2.39**	K_2CO_3	-35	Tol.	24	19%	84
127	**2.39**	CsOH	-40	Tol.	24	87%	89

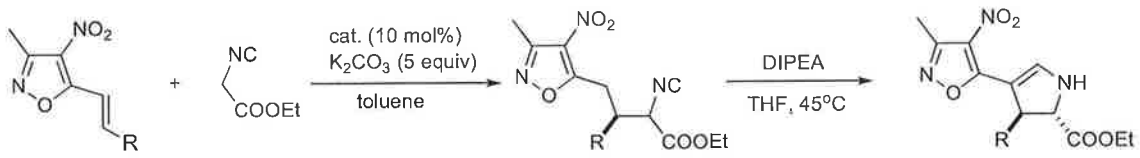
[a] Determined by ^{1}H-NMR of the crude mixture.[b] Determined by chiral stationary HPLC on the major diastereoisomer of compound **2.20a**. [c] 4 equiv of ethylisocyanoacetate was used. [d] 6 equiv of ethylisocyanoacetate was used. [e] The reaction was performed using 2mL of solvent. [f] Reaction was performed under anhydrous conditions, without increasing the *ee*. [g] The reaction was performed using 0.5mL of toluene. [h] 2equiv of base was used instead of 5eq. without increasing the *ee*. [i] Increasing the amount of catalyst (50 mol%), the *ee* decreased. [l] 5 mol% of catalyst was used. [j] 7:3 ratio of solvents was used without incresing the *ee*. [k] The reaction was performed using 10 mol% of catalyst, 5 equiv of ethylisocyanoacetate, 5 equiv of K_2CO_3 in 0.5mL of toluene.

Table 2. Results from the screening of cinchonidine derived catalysts **2.28**-**2.29**.

At the onset of this study, we have reacted styrylisoxazole **2.17** with ethylisocyanoacetate **2.18** in presence of various inorganic bases and suitable solvents. When catalyst **2.28** was used in presence of Cs_2CO_3 at -20°C, compound **2.20a** was obtained in 79% *ee* (**Table 2**, entry 21). Other bases as KOH and K_3PO_4 50% w/w at the same temperature gave 78 and 76% *ee* respectively but lower conversion (**Table 2**, entries 15 and 19). In a mixed solvent system, toluene/CH_2Cl_2 (9:1) the *ee* value decreased (**Table 2**, entries 16 and 18). Catalyst **2.29** gave its best enantioselectivity of 62% when the reaction was performed at -20°C in presence of K_2CO_3 (**Table 2**, entry 30). Using Cs_2CO_3 and CsOH as bases under the same conditions of temperature and solvent lower enantiomeric excess were obtained (**Table 2**, entries 35 and 33). When catalyst **2.30** was used in the presence of Cs_2CO_3 at -20°C compound **2.20a** was obtained in 49% *ee* (**Table 2**, entry 41); using CsOH at -20°C the enantioselectivity improved to 68% *ee* even if the conversion was lower (**Table**

2, entry 44). Lowering the reaction temperature to -42°C and -60°C was detrimental for the enantiomeric excess (**Table 2**, entries 45, 46). Catalyst **2.31** gave 86% *ee* in the presence of Cs_2CO_3 at -20°C (**Table 2**, entry 48); lowering the reaction temperature to -35°C and to -45°C did not increase the *ee* (**Table 2**, entries 56 and 62). In a mixed solvent system as toluene/TBME (7:3) or toluene/CH_2Cl_2 (7:3) the *ee* decreased to 83 and 80% (**Table 2**, entries 49-50). K_2CO_3 was an equally effective base affording **2.20a** in 85% *ee* at -20°C (**Table 2**, entry 52); even in this case, lowering the temperature was detrimental for the enantiomeric excess. A different behavior was observed when using K_3PO_4 50% w/w as the base. The enantioselectivity of **2.20a** was 86% *ee* at -20°C (**Table 2**, entry 53), lowering the reaction temperature to -35°C allowed the attainment of an enantiomeric excess of 87% (**Table 2**, entry 60). When the reaction was carried out at -78°C, using as base CsOH and NaOH 33% w/w, the enantiomeric excess was 82 and 86% respectively, but the conversion was low despite the long reaction time (**Table 2**, entries 69-70). Catalyst **2.32** allowed the enantioselectivity of compound **2.20a** to reach 91% *ee* using K_2CO_3 as base at -20°C (**Table 2**, entry 83). In a mixed solvent system or changing the reaction concentration the *ee* value did not increase (**Table 2**, entries 84 and 87-89). Decreasing or increasing the reaction temperature allowed the enantioselectivity of compound **2.20a** to reach only 76-80% *ee* (**Table 2**, entries 71-73 and 99). K_2CO_3 50% w/w at -20°C also proved to be an almost equally effective base, affording **2.20a** in 89% *ee* (**Table 2**, entry 80). The use of catalyst **2.33**, **2.34** and **2.35** in presence of Cs_2CO_3 at -20°C gave **2.20a** respectively in 60, 43 and 60% *ee* (**Table 2**, entries 108, 109 and 111). At this point of our study we performed the reaction with catalyst **2.36**, **2.37** and **2.38** using K_2CO_3 at -20°C to give **2.20** respectively in 68, 76 and 81% *ee* (**Table 2**, entries 112-114). Finally the use of catalyst **2.39** at -20°C in presence of K_2CO_3 as base gave the desired compound in 93% *ee* (**Table 2**, entry 115). By lowering the reaction temperature to -35°C, the enantioselectivity decrease to 84% (**Table 2**, entry 126). Therefore we found the optimum conditions required the use of 10 mol% of *N*-(3,5-bis(trifluoromethyl)benzyl) cinchonidinium bromide **2.39**, as catalyst, 5 equiv of K_2CO_3, 5 equiv of ethylisocyanoacetate in 0.5mL of toluene at -20°C, which ensured a high conversion of **2.17** and gave compound **2.20a** in 96% *ee* (**Table 2**, entry 116).

The scope of the reaction was shown by reacting styrylisoxazoles **2.17a-n** with ethylisocyanoacetate under the catalysis of **2.39** and the sterically demanding bis *tert*-butyl ammonium bromide **2.38** (**Table 3**).[15]



2.17a-n **2.18** **2.19a-n** **2.20a-n**

Entry	2.17	R	Cat.	t(h)	2.19	Yield[%][a]	2.20	Yield[%]	ee[%][b]
1	**2.17a**	C_6H_5	**2.39(2.39')**	78	**2.19a**	81(79)	**2.20a**	67(72)	97 (74)
2	**2.17b**	4-MeC_6H_4	**2.39(2.39')**	52	**2.19b**	81(77)	**2.20b**	76(75)	93 (62)
3	**2.17c**	4-ClC_6H_4	**2.38(2.38')**	58	**2.19c**	80(70)	**2.20c**	62(59)	97(56)
4	**2.17d**	2-$MeOC_6H_4$	**2.38(2.38')**	120	**2.19d**	75(75)	**2.20d**	66(64)	97(92)
5	**2.17e**	4-FC_6H_4	**2.38**	25	**2.19e**	80	**2.20e**	73	88
6	**2.17f**	2-furyl	**2.39**	183	**2.19f**	75	**2.20f**	63	90
7	**2.17g**	4-$MeOC_6H_4$	**2.38**	48	**2.19g**	72	**2.20g**	69	89
8	**2.17h**	3-MeC_6H_4	**2.39**	22	**2.19h**	78	**2.20h**	54	94
9	**2.17i**	4-$NO_2C_6H_4$	**2.39**	46	**2.19i**	15	**2.20i**	58	88
10	**2.17j**	3-BrC_6H_4	**2.38**	30	**2.19j**	64	**2.20j**	61	56
11	**2.17k**	2,3-ClC_6H_3	**2.38**	48	**2.19k**	61	**2.20k**	58	88
12	**2.17l**	Naphthyl	**2.38**	65	**2.19l**	80	**2.20l**	64	86
13	**2.17m**	4-CNC_6H_4	**2.38**	48	**2.19m**	76	**2.20m**	65	86
14	**2.17n**	Isopropyl	**2.39**	48	**2.19n**	88	**2.20n**	64	77

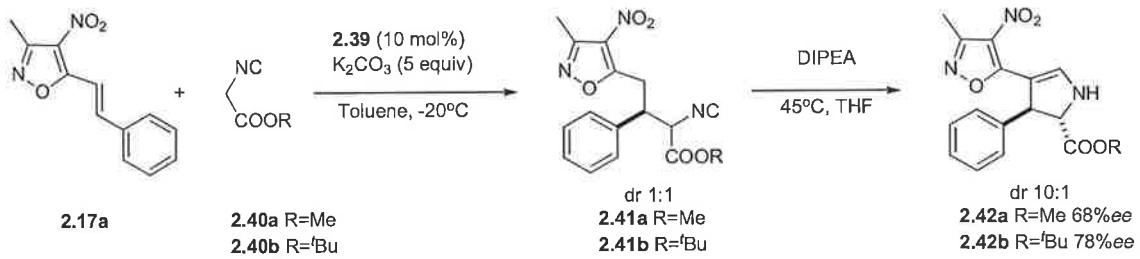
[a] Isolated yield after chromatography on silica gel. [b] Determined by chiral stationary phase HPLC on the major diastereoisomer of compound **2.20a-n**. [c] The reaction was performed using 10 mol% of catalyst, 5 equiv of ethylisocyanoacetate, 5 equiv of K_2CO_3 in 0.5mL of toluene.

Table 3. Catalytic asymmetric addition of ethylisocyanoacetate to styrylisoxazoles **2.17a-n**.[c]

The results collected pointed out the following facts: i) compounds containing either electron withdrawing or electron donating groups on the phenyl were equally good substrates (**Table 3**, entries 2-5 and 7-13); ii) substrates containing aromatic heterocycles were also good substrates giving product in good *ee* and yield (**Table 3**, entry 6); iii) the presence of a bulky substituent gave good enantiomeric excess (**Table 3**, entry 12); iv) the use of *quasi*-enantiomeric catalyst **2.38'** derived from cinchonine gave excellent

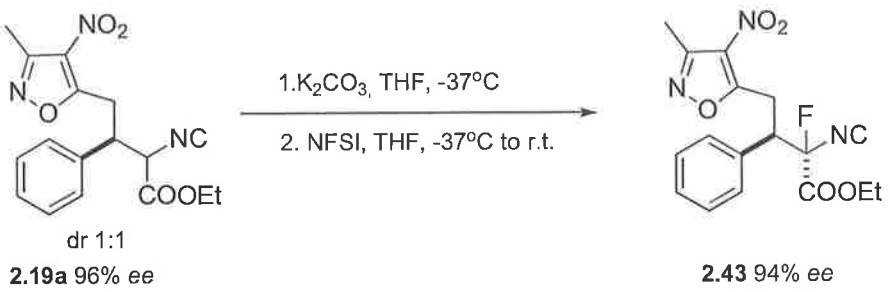
enantiomeric excess in the case of compound ***ent*-2.20d** and but less so with ***ent*-2.30c** (**Table 3**, entries 3-4), while catalyst **2.39'** did not allow preparation of compounds ***ent*-2.20a** and ***ent*-2.20b** in comparable excellent enantiomeric excess to **2.39** (**Table 3**, entries 1-2).

Having established a highly enantioselective procedure for the conjugate addition of ethylisocyanocatate **2.18** to styrylisoxazoles **2.17a-n**, we explored other isocyanoacetates as the nucleophile. Initially, styrylisoxazole **2.17a** was reacted with methylisocyanoacetate **2.40a** (**Scheme 7**). Delightfully, this reaction proceeded at -20°C to give the expected adduct **2.41a** in 73% yield (dr 1:1) and 68% *ee* calculated on cyclic compound **2.42a** obtained in 67% yield. Similarly, **2.17** reacted with *tert*-butylisocyanoacetate **2.40b**, giving product **2.41b** in only 48% yields (dr 1:1), and 78% *ee* (calculated on compound **2.42b**) (**Scheme 7**).



Scheme 7. Catalytic asymmetric addition of methyl and *tert*-Butyl isocyanoacetates to 5-styrylisoxazole **2.17a**.

Enantioenriched compound **2.19a** was employed for the preparation of fluorinated compound **2.43** (**Table 4**).



Entry	Fluorinating agent	Base	T (°C)	Solvent	Yield (%)
1	NFSI	LDA	-78 to rt	THF	-[a]
2	NFSI	DIPEA	rt	THF	-[b]
3	NFSI	K_2CO_3	-37 to rt	THF	67
4	Selectfluor®	-	rt	CH_3CN	-[b]

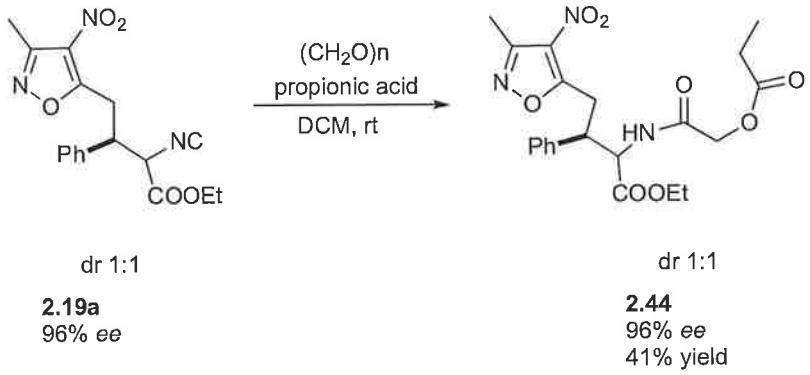
[a]Degradation was observed. [b]Starting material was recovered

Table 4.

Compound **2.19a** was firstly treated with LDA at -78°C using NFSI (*N*-fluorobenzenesulfonimide) as fluorinating agent but without good result (**Table 4**, entry 1). When the reaction was performed using DIPEA as base at room temperature only starting material was recovered (**Table 4**, entry 2). Even using Selectfluor® as fluorinating agent no conversion was observed. Finally the desired compound **2.43** was obtained using 1.2 equiv of K_2CO_3 as base at -37°C in dry THF and 5 equiv of NFSI (**Table 4**, entry 3) in 67% yield, in 94% *ee*. Compound **2.43** was obtained in one diastereoisomer as shown in the ^{19}F NMR spectrum, where only one peak was detected at -128.2 ppm. The ^{1}H NMR spectrum showed an unfree rotation of the molecule, even when the spectrum was carried out at higher temperatures such as 40°C and 60°C.

Compound **2.19a**, which has a free isonitrile moiety, was also reacted in multicomponent reactions (MCRs); the Passerini and Ugi reactions.

First, the Passerini reaction of **2.19a,** 1.5 equiv. of paraformaldehyde and 1.1 equiv. of propionic acid in CH_2Cl_2 was studied. Product **2.44** was obtained as a mixture of two diastereoisomers (dr 1:1), in only 41% yield; adding ethyl ether one of the two diastereoisomers was obtained as a white solid (**Scheme 8**).[16]



dr 1:1

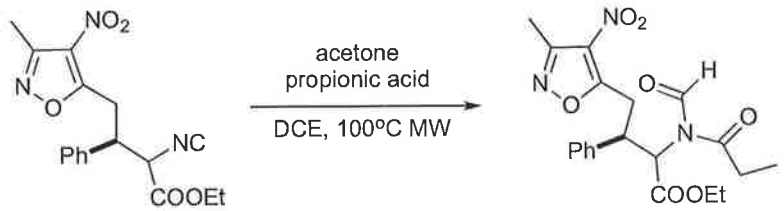
2.19a
96% *ee*

dr 1:1

2.44
96% *ee*
41% yield

Scheme 8. Passerini reaction on compound **2.19a**.

When acetone was used instead of paraformaldehyde only starting material was recovered even when the reaction was heated at 85°C in dichloroethane for 15 h. Heating the reaction under microwave (100°C for 6h), we noticed the formation of compound **2.45** in 20% yield, not the desired Passerini product but the Danishefsky compound, maybe due to the sterical hindrance of the acetone (**Scheme 9**).



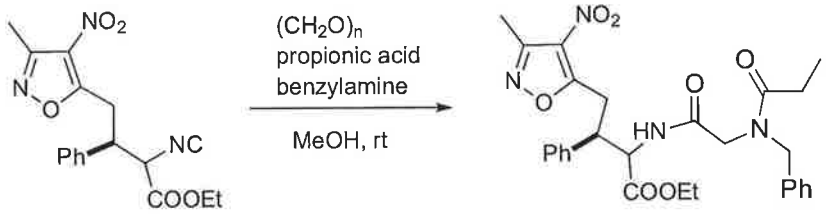
dr 1:1

2.19a

2.45

Scheme 9. Formation of Danishefsky compound **2.45** from **2.19a**.

Further, we investigated the Ugi reaction of **2.19a**, using 1.5 equiv. of paraformaldehyde, 1.1 equiv. of propionic acid, 1.5 equiv. of benzylamine in MeOH at r.t.. Compound **2.46** was obtained in 36% yield as a mixture of two inseparable diastereoisomers (dr 2:1) and the two corresponding rotamers (**Scheme 10**).[16]



dr 1:1

2.19a (*racemic*)

dr 2:1

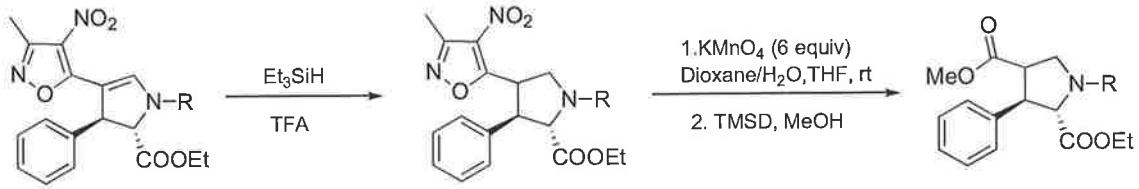
2.46

Scheme 10. Ugi reaction on compound **2.19a**.

With compound **2.20a** in hand, the next step was to reveal the carboxylic functionality, which was converted to the corresponding methyl ester **2.48** to facilitate the isolation by chromatography on silica gel. First compound **2.20a** was treated with $KMnO_4$ in acetone/water solution (3.5:1) for 1h at room temperature. Unfortunately the desired acid was not isolated. **2.20a** was then reacted with NaOH 1M in THF at 100°C, but no trace of the dicarboxylic acid was observed.

At this point we decided to reduce first the double bond using Et_3SiH in TFA to give **2.47** in 73% yield and then work on the oxidation of the isoxazole moiety.[14]

Different conditions for the oxidation were used, as shown in **Table 5**.



2.20a

2.47

2.48

Entry	R	Solvent	Oxidant	Time	T(°C)	Yield (%)
1	H	THF	$KMnO_4$ H_2O/acetone	3 hours	rt	-[f]
2	Fmoc	THF	$KMnO_4$ H_2O/acetone	1 hours	rt	-[e]
3	H	THF	$KMnO_4$ H_2O/Dioxane	45 min	rt	11

4	H	H_2O/Dioxane	$KMnO_4$ H_2O/Dioxane	45 min	rt	10[a]
5	H	H_2O/Dioxane	$KMnO_4$ H_2O/Dioxane	45 min	0	10[b]
6	H	THF	$KMnO_4$ H_2O/THF	10 min	-78	9
7	H	Benzene	$KMnO_4$ Benzene 18-crown-6[c]	15 min	rt	-[f]
8	H	Toluene	Benzyltriethylammonium chloride[d]/$KMnO_4$	15 min	rt	-[f]
9	H	Toluene	Tetrabutylammonium periodate[d] /$KMnO_4$	15 min	rt	-[f]
10	H	Toluene	Tetrabutylammonium bromide[d]/$KMnO_4$	15 min	rt	-[f]
11	H	Toluene	Tetrabutylammonium iodide[d]/$KMnO_4$	15 min	rt	-[f]

[a]1 equiv of *p*-toluenesulfonic acid was added when **2.47** was dissolved in H_2O/Dioxane. $KMnO_4$ dissolved in H_2O/Dioxane was added. The solution was stirred 45 min at rt then 1 equiv of HCl was added. [b]5 equiv of HCl was added to **2.47** dissolved in H_2O/Dioxane. [c]18-crown-6 was added to $KMnO_4$ in Benzene until the oxidant agent was dissolved completely. [d]To a solution of 0.1 mmol of **2.47** in THF and 5 equiv of $KMnO_4$, 30 mol % of catalyst was added. [e]mixture of diastereoisomers was observed. [f]No trace of desired product was observed.

Table 5.

Unfortunately the desired product **2.48** was obtained as 2 diastereoisomers (dr 2:1) only in 11% yield using 6 equiv of $KMnO_4$ dissolved in dioxane/water in THF at rt for 1h (**Table 5**, entry 3). With the aim to improve the yield other reaction conditions were tried but without any good result. When the reaction was carried out at -78°C for 10 min. product **2.47** was obtained in 9% yield (**Table 5**, entry 6). When the reaction solvent was changed to dioxane/water instead of THF the desired product was isolated in 10% yield, even changing the temperature (**Table 5**, entries 4 and 5).

2.4 Conclusions.

In conclusion, we have described a good enantioselective Michael addition under operationally simple conditions and mild PTC catalysis, which could serve as valuable building blocks and as templates of high potential synthetic utility.

2.5 References.

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Chapter 3: A highlight on polycyclic ethers: A class of compounds isolated from marine sources.

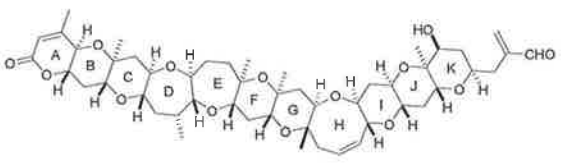
3.1 Origin, structures and activities of polycyclic ethers from marine microorganisms.

The polycyclic ethers are one of the most characteristic and spectacular classes of compounds isolated from marine sources. These molecules are produced by marine microorganisms, mostly by unicellular flagellated algae called dinoflagellates. The first fused polycyclic ether to be structurally determined was brevetoxin-B **3.1** (**Figure 1**) in 1981[1]. Since then, various natural products with similar skeletons have been structurally elucidated using modern spectroscopic techniques.[2] These molecules are made up of a single carbon chain locked into a long semirigid ladder-like structure. The striking regularity with which the oxygen atoms bridge the nanoscale polycyclic framework is a remarkable feature of these molecules: cyclic ethers of sizes ranging from five- to nine-membered rings all fuse in a *trans/syn/trans* fashion. Despite this common polycyclic motif, they show diverse biological activities with extreme potency. Brevetoxins (**3.1**,[1] **3.2**[3]) are potent ichthyotoxins (**3.2**:LC_{100} 4 ng/mL to guppies) and were isolated from the dinoflagellate *Karenia* (formerly *Gymnodinium*) *breve*, blooms of which cause a phenomenon known as "red tide". Red tides giving rise to these toxins have killed great numbers of fish and caused intoxication in humans. These molecules exert their toxicity by binding to the voltage-sensitive sodium channels (VSSC) of excitable membranes, causing them to open, thereby allowing sodium ion influx.[4] Hemibrevetoxin-B (**3.4**)[5] and brevenal (**3.6**)[6] were found in the same organism, and their molecular sizes are about one-half of that of brevetoxins. Hemibrevetoxin-B (**3.4**) was reported to cause the same characteristic rounding of cultured neuroblastoma cells as brevetoxins. Significantly, it was demonstrated that **3.6** competitively displaced brevetoxin from its binding site on VSSC and antagonized the toxic effect of brevetoxins in fish. Thus, **3.6** has the potential to serve as a therapeutic agent in the treatment of brevetoxin poisoning. Ciguatoxins (**3.3**,[7] **3.5**,[8] **3.7**[9])[10] were isolated as the principal toxins in widespread seafood poisoning known as ciguatera.[11] More than 20 000 people suffer annually from ciguatera, making it

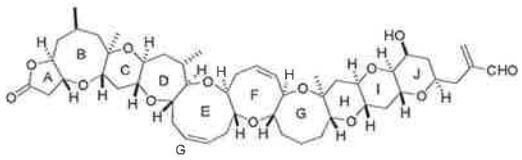
one of the most common food poisonings of nonbacterial origin. The toxins, generated by the epiphytic dinoflagellate *Gambierdiscus toxicus*,[12] are transferred through the aquatic food chain. Approximately 100 species of fish cause ciguatera; these ciguateric fish look, taste, and smell the same as uncontaminated fish. Ingestion of affected fish leads to neurological, gastrointestinal, and cardiovascular disorders, which may last up to one month or more and may reoccur periodically. Ciguatoxins and brevetoxins share a specific binding site on VSSC, although ciguatoxins bind 10 times more strongly than brevetoxins.[4,13-15] Moreover, the lethal potencies of ciguatoxins (LD_{50} = 0.25-4 μg/kg), determined by intraperitoneal injection into mice, are much greater than those of brevetoxins (LD_{50} > 100 μg/kg).[14] The low fatality rate in ciguatera is due solely to the minute concentration of ciguatoxins in fish flesh. Some strains of *Gambierdiscus toxicus* produce not only ciguatoxins, but also other polycyclic ethers such as gambierol (**3.8**)[16] and gambieric acids (**3.10**).[17] Gambierol (**3.8**) exhibits toxicity toward mice (LD_{50} = 50 μg/kg) with symptoms resembling those of ciguatoxins, inferring the possibility that **3.8** is involved in ciguatera poisoning. Most recently with the use of taste cells, the molecular target of **3.8** was identified to be the voltage-sensitive potassium channel.[18] On the other hand, gambieric acid (**3.10**) is nontoxic to mice; nevertheless, **3.10** is a potent antifungal. The antifungal activity of **3.10** is 2000 times greater than that of amphotericin B. The notorious red tide dinoflagellate *Gymnodinium mikimotoi*, which is representative of the species that causes damage worldwide, produces gymnocin-A (**3.9**).[19] Gymnocin-A is approximately 250 times less ichthyotoxic than 42-dihydrobrevetoxin-B but is cytotoxic to P388 mouse leukemia cells (ED_{50} = 1.3 μg/mL). Yessotoxin (**3.12**) was isolated as one of the causative toxins in diarrheic shellfish poisoning, with *Protoceratium reticulatum* being identified as the biogenetic origin of **3.10**.[20] The polycyclic skeleton of adriatoxin (**3.11**) is identical to that of the A-J-ring system of **3.12** but lacks the K-ring and its side chain.[21] As these toxins have shown potent mouse lethality, contamination of bivalves by **3.11** and **3.12** poses a worldwide problem to human health as well as to the shellfish industry. Most recently an extremely potent cytotoxic agent, protoceratin II (**3.13**), was isolated from the culture broths of *Protoceratium reticulatum* and characterized as having a yessotoxin skeleton substituted with two arabinosides.[22] Remarkably, IC_{50} values of **3.13** against human cancer cell lines were reported to be less than 0.5 nM. These

polycyclic ethers have attracted intense interest from biologists and chemists alike because the novel and specific activities of these toxins may present a unique opportunity for investigation of unknown biological events as well as application as important chemotherapeutic agents. Although many investigations have focused on elucidating their biological targets, receptor proteins have only been identified for brevetoxins, ciguatoxins, and gambierol as mentioned above,[4,13-15,18,23] mainly due to their limited availability from natural sources. Over the past two decades a number of laboratories have attempted the chemical construction of these compounds, motivated by their unusual molecular architecture, biological activity, and association with the catastrophic effects of red tide phenomena and food poisoning.[24] Their exquisitely complex structures have served as the inspiration for development of new methodologies in organic synthesis and as an elegant platform for exhibiting the creativity of the modern organic chemist. In 1995 Nicolaou, a pioneer in the field of polyether synthesis, reported the first total synthesis of brevetoxin-B (**3.1**).[25] This major advance was followed by the synthesis of brevetoxin-A (**3.2**) by the same laboratory in 1998.[26] In the last years many laboratories have contributed to even more rapid progress.[27]

These efforts culminated in the total syntheses of ciguatoxin CTX3C (**3.5**) by Hirama (2001),[28] gambierol (**3.8**), synthesized independently by Sasaki (2002),[29] Kadota/Yamamoto (2002),[30] and Rainier (2005),[31] brevetoxin-B (**3.1**) by Nakata (2004)[32] and Kadota/Yamamoto (2005),[33] gymnocin-A (**3.9**) by Sasaki (2003)[34] and brevenal (**3.6**) by Sasaki (2006). These landmark achievements were made possible by the development of a number of important reactions and methodologies. The large and complex structures of these molecules necessitate a highly efficient synthetic strategy with excellent material throughput and a minimum number of synthetic transformations.



Brevetoxin-B (3.1)



Brevetoxin-A (3.2)

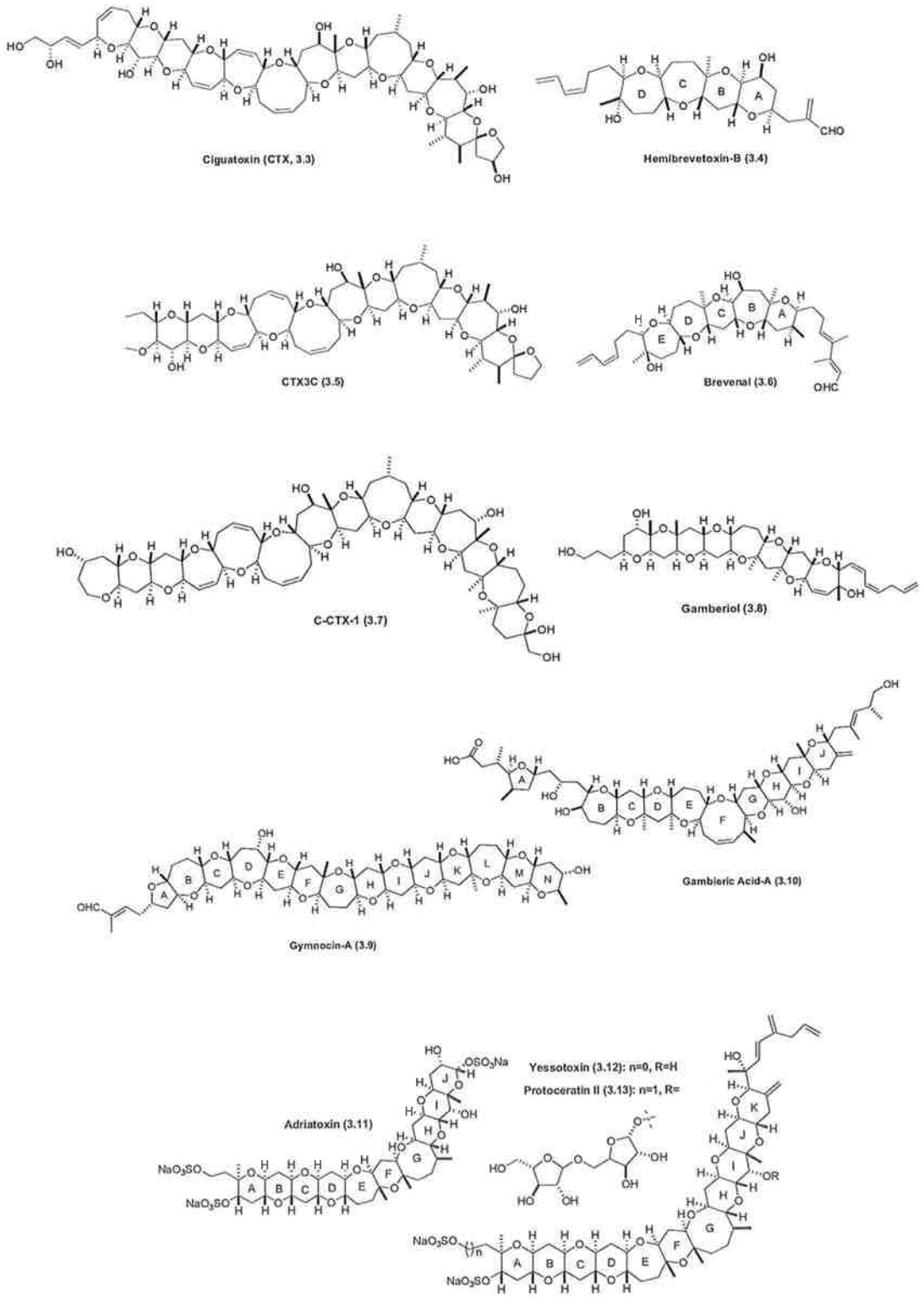
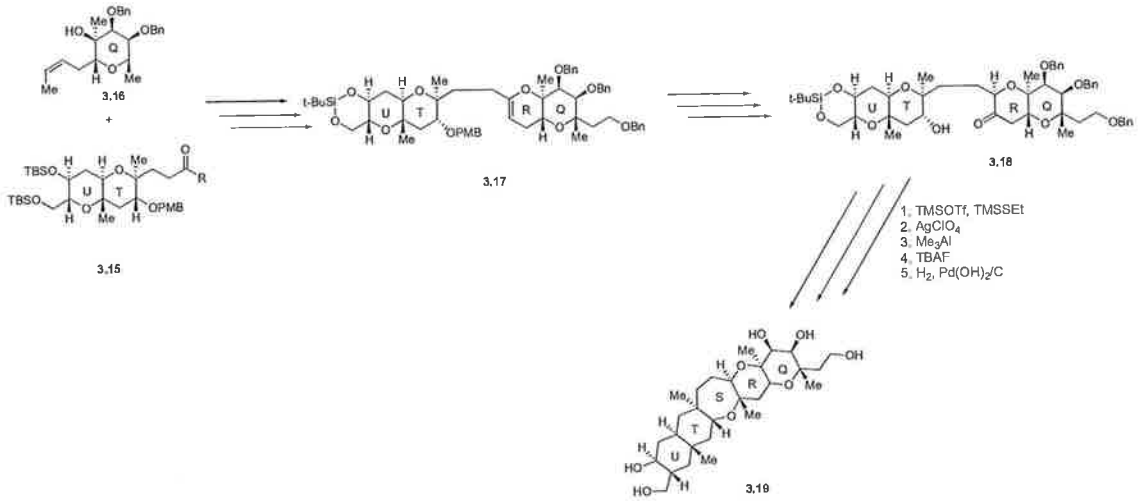


Figure 1. Polycyclic ethers isolated from marine microorganisms.

3.2 Strategy for the synthesis of oxepanes contained in natural products.

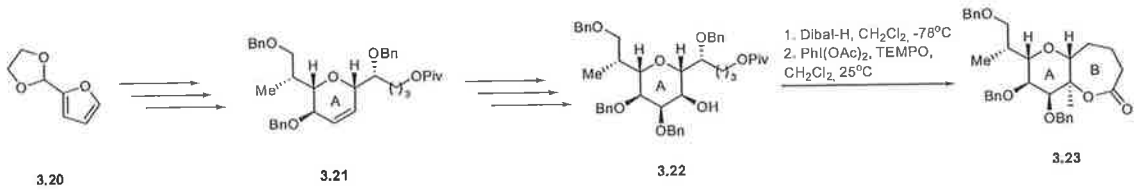
In the last two years few synthetic strategies of oxepanes contained in natural products were reported. Nicolaou and co-workers in 2010 reported a synthetic strategy toward the QRSTU ring system **3.19** of the marine-derived biotoxin maitotoxin **3.14** (**Figure 2**). The convergent route to these maitotoxin fragments involved coupling of UT and Q building blocks **3.15** (obtained from 2-deoxy-d-ribose) and **3.16** (obtained from d-ribose) followed by ring-closing metathesis to afford enol ether **3.17**, whose elaboration to the targeted QRSTU ring system **3.19** required its conversion to hydroxy ketone **3.18** (**Scheme 1**). The latter compound **3.18** was transformed to the final product through a hydroxy dithioketal cyclization, performed in the presence of TMSSEt and TMSOTf and followed by reaction with $AgClO_4$, $NaHCO_3$ in $MeNO_2$. The resulting *O,S*-mixed ketal underwent oxidation/methylation to install the last of the five methyl groups contained within the target molecule **3.19**.

Figure 2. Maitotoxin structure (**3.14**).



Scheme 1.

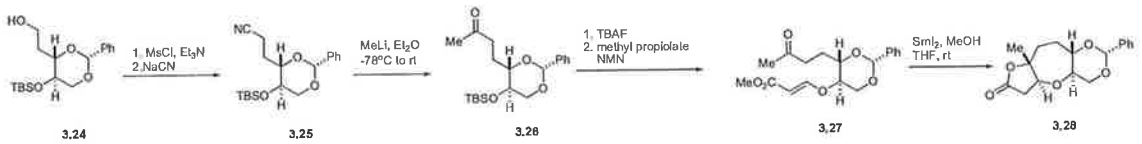
Previously the same group synthesised the AB ring of Maitotoxin **3.14**. Starting from the furfural-derived ethylene ketal **3.20**, compound **3.21** was obtained in a nine-step synthesis.[36] From **3.21** the desired hydroxyl compound **3.22** was obtained involving stereoselective epoxidation (*m*-CPBA, 71% yield, ca. 5:1 *dr*), epoxide opening with $BnOH\text{-}BF_3{\bullet}OEt_2$ to afford tetrabenzyl ether (91% yield), and Swern oxidation-reduction. Removal of the pivaloate group of the hydroxyl compound **3.22** in presence of Dibal-H in CH_2Cl_2 at -78°C, (83% yield) followed by oxidative lactonization using $PhI(OAc)_2$ and TEMPO led to AB ring system **3.23**.



Scheme 2.

In 2009 Sasaki, Fuwa and co-workers performed a highly stereocontrolled, convergent synthesis of the A/B-ring fragment of gambieric acid **3.10**.[37] The synthesis of seven membered ring B started with mesylation of the alcohol **3.24**[38] followed by displacement with NaCN to give nitrile **3.24** (**Scheme 3**). Exposure of **3.24** to MeLi in Et_2O at -78 to

0°C smoothly afforded methyl ketone **3.26** in 85% yield after acidic workup. Desilylation of **3.26** followed by hetero-Michael reaction of the derived alcohol using methyl propiolate and *N*-methylmorpholine (NMM) provided *β*-alkoxy acrylate **3.27**. According to the Nakata protocol,[39] treatment of **3.27** with SmI_2 in the presence of methanol in THF at room temperature cleanly furnished lactone **3.28** in 74% yield as a single isomer.



Scheme 3.

3.3 Aim.

The aim of the proposed work is the establishment of a new strategy for the preparation of medium sized oxepanes **3.29**, oxocanes **3.30**, and oxonanes **3.31** (**Figure 3**).

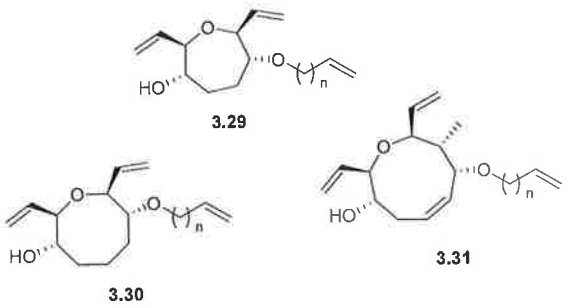
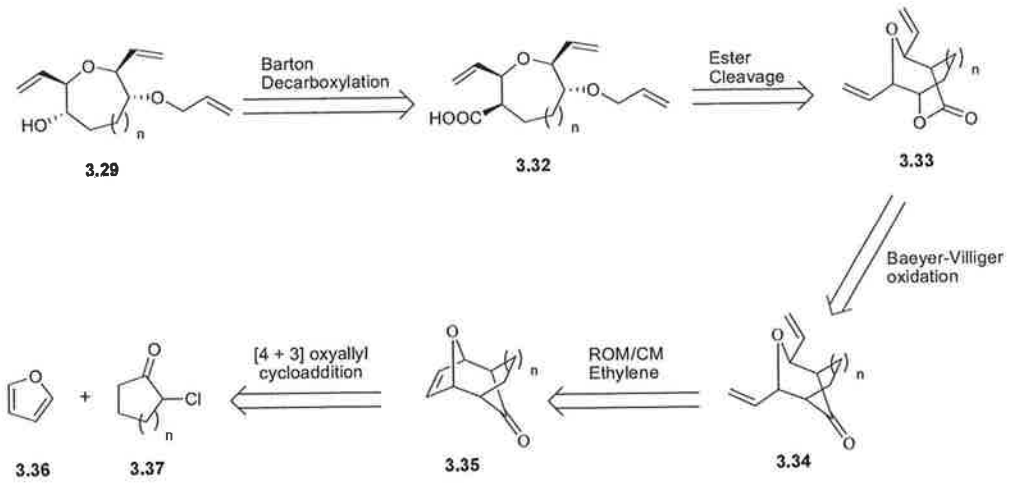


Figure 3. Structure of compounds **3.29**, **3.30** and **3.31.**

For these targets, a [4 + 3] cycloaddition (**Scheme 4**) to generate the polycyclic strained intermediate was required. A disconnection of compound **3.29** indicated that the furan **3.36** and α-chloroketone **3.37** were ideal starting materials. In our plan, compound **3.29** could be obtained from **3.32** by a Barton decarboxylation. In turn, compound **3.32** could be prepared by Lewis acid mediated hydrolysis of ester **3.33** that is obtained from a

Baeyer-Villiger oxidation of ketone **3.34**. The key step in this plan is the ROM/CM of cycloadduct **3.35** to masked oxepane **3.34**.

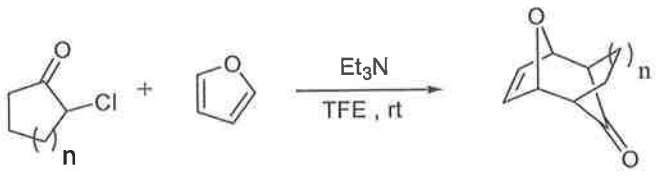


Scheme 4.

3.4. Results and Discussion.

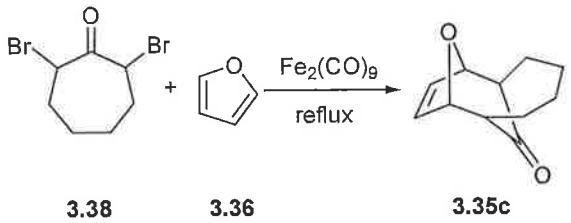
We began our studies by a [4+3] cycloaddition reported in the literature between furan **3.36** and α-chlorocycloketones **3.37a-b** under Folisch conditions[40] (**Scheme 5**).

Compounds **3.35a** and **3.35b** were obtained in 90% and 93% yield respectively by reacting 5 equiv of **3.38** and 1 equiv **3.39a** or **3.39b** in the presence of 2 equiv Et_3N and 20 mL of TFE at rt.



Scheme 5.

When we tried to synthesise cycloadduct **3.35c** using the same conditions, only starting material was recovered. The bicyclic **3.35c** was obtained in 50% yield starting from 2,7-dibromocycloheptanone **3.38**[41] and furan **3.36** in presence of 1.2 mmol of $Fe_2(CO)_9$ (**Scheme 6**).[42]



3.38 **3.36** **3.35c**

Scheme 6.

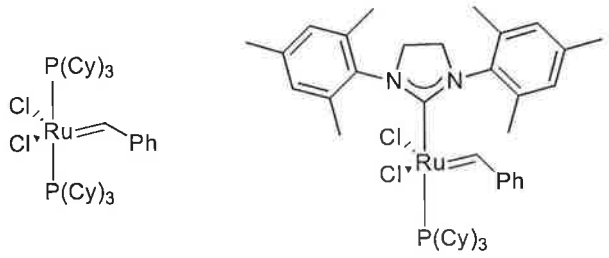
The cycloadducts **3.35a**, **3.35b** and **3.35c** showed the presence of two functional groups: a ketone and an alkene. We decided first to react the ketone with the aim of obtaining a lactone by Baeyer Villiger oxidation.[43]

After a few unsuccessful attempts using *m*-chloroperoxybenzoic acid (*m*-CPBA),[44] H_2O_2 and Oxone®,[45] we decided to focalize our synthesis, first, on the alkene moiety performing a ring opening metathesis/cross metathesis (ROM/CM).

When compound **3.35a** was reacted with 10 mol% of Grubbs' II generation catalyst (**Figure 4**) and ethylene under pressure (> 500 psi), compound **3.40a** was obtained in only 20% yield and starting material **3.35a** was recovered. This was explained by the fact that the opening products **3.40a** could undergo ring closing metatheses (RCM) to regenerate the starting product.

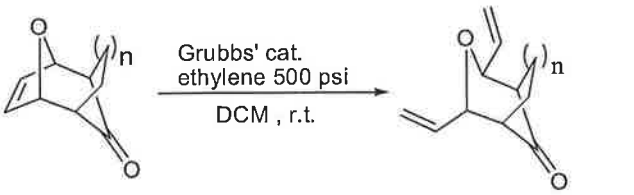
When the reaction was performed in presence of 10 mol% Grubbs' I generation catalyst (**Figure 4**) and ethylene (> 500 psi) in CH_2Cl_2 at rt the desired products **3.40a** and **3.40b** were obtained in 90% and 77% yield starting from **3.35a** and **3.35b** respectively (**Scheme 7**).

The ROM/CM conditions did not led to any product when applied to compound **3.35c**, compound **3.40c** was obtained in only 8% yield when the mixture was heated to 40°C.



Grubbs' I generation catalyst **Grubbs' II generation catalyst**

Figure 4. Grubbs' I and II generation catalyst.



3.35a n=1
3.35b n=2
3.35c n=3

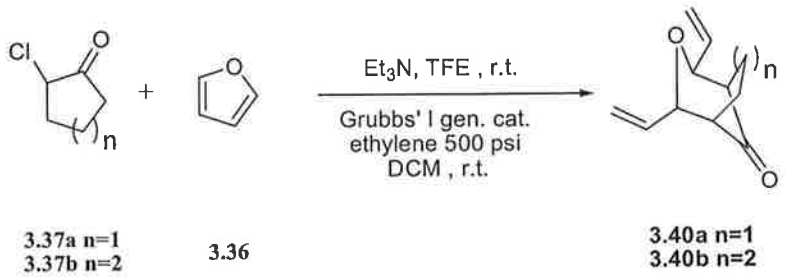
3.40a n=1 90% Yield
3.40b n=2 77% Yield
3.40c n=3 8% Yield

Scheme 7.

With these results in hand we decided to perform the [4 + 3] cycloaddition and the ROM/CM in a one-pot fashion.

Firstly, the reaction was performed using the conditions described by Folisch (**Scheme 8**), adding 10 mol% of Grubbs' I generation catalyst dissolved in dry CH_2Cl_2 and ethylene.

The desired product **3.40a** was obtained in 50% yield and the cycloadduct **3.35a** was also observed. To drive the reaction to completion 25 mol% of Grubbs' catalyst was required. This could be explained as reported in the literature, the activity of Grubbs' catalyst is reduced in the presence of an amine due to the interaction between the lone pair of the amine itself and the ruthenium.[46]



3.37a n=1
3.37b n=2

3.36

3.40a n=1
3.40b n=2

Scheme 8.

With the aim to reduce the amount of Grubbs' catalyst, an expensive reagent, we considered the possibility of using different bases and solvents, as showed in **Table 1,** to perform the [4 + 3] cycloaddition.

Entry	Solvent	Base	Yield
1	CH_2Cl_2	NEt_3 (2 mmol)	Only SM
2	THF (20 mL)	NEt_3 (2 mmol)	Only SM
3	CH_3CN (20 mL)	NEt_3 (2 mmol)	Only SM
4	-	NEt_3 (2 mmol)	20%
5	EtOH (20 mL)	NEt_3 (2 mmol)	90%
6	CF_3CH_2OH (20 mL)	PPh_3 (2 mmol)	Only SM

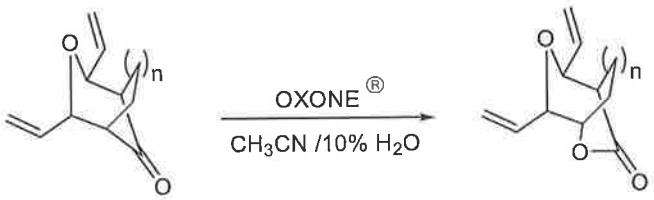
Table 1: Cycloaddition of **3.37a** with furan **3.36** using different solvents and bases.

After these results we tried to perform the one pot reaction using the same conditions as entry 5 but unfortunately without good results.

We decided to reduce the amount of NEt_3 and TFE used for the initial cycloaddition without decreasing the yield of product **3.35a**. The best conditions found were when the cycloaddition between 1 equiv of α-chloropentanone **3.37a** and 5 equiv of furan **3.36** was carried out in the presence of 1.2 equiv of Et_3N and 1 mL of TFE.

Using these conditions and adding 5 mol% of Grubbs' I generation catalyst dissolved in CH_2Cl_2 and ethylene under pressure (>500 psi), compound **3.40a** was obtained in 92% yield. When the same reaction was performed starting from **3.37b** the ring opened product **3.40b** was obtained in only 12% yield.

With compounds **3.40a** and **3.40b** in hand, we investigated the next step, the Baeyer Villiger oxidation. Initial attempts were made by reacting compound **3.40a** and *m*-CPBA with $Sc(OTf)_3$ as Lewis Acid,[47] but starting material was recovered. When the reaction was performed in presence of 5 equiv of Oxone® in CH_3CN/10% H_2O, the desired lactones **3.41a** and **3.41b** were obtained in 92% and 40% yields respectively (**Scheme 9**).



3.40a n=1
3.40b n=2

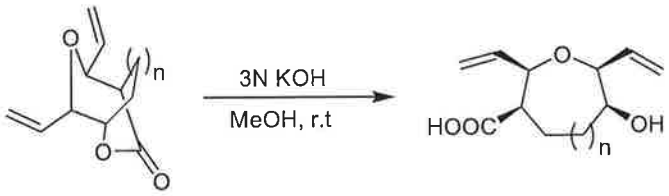
3.41a n=1
3.41b n=2

Scheme 9.

It is worthy of note that this reaction has a very important role in the synthetic plan leading to the desymmetrization molecules **3.40a** and **3.40b**.

Our next aim was the ring opening of the lactones **3.41a** and **3.41b** to obtain the acid and the *O*-alkoxy in the *trans* position.

Firstly compound **3.41a** was treated with 2 equiv. of $AlBr_3$, with the aim of producing a transient carbocation, and 16 equiv of 3-buten-1-ol were added, but starting material was recovered.[48] Next **3.41a** was reacted in the presence of allylalcohol pretreated with NaH in dry THF but the hydroxy acid **3.42a** was obtained in 60% yield instead of the desired product. After this result the δ-lactone **3.42a** was treated with 5 equiv. of KOH 3N in MeOH and carefully neutralized with HCl to afford the compounds **3.42a** and **3.42b** in 92% and 80% yield respectively (**Scheme 10**).[49] After crystallization of **3.42a** in $CHCl_3$, it was analyzed by X-ray spectroscopy to show the position of all the substituents on the oxo ring are in *cis* position (**Figure 5**).



3.41a n=1
3.41b n=2

(±)-3.42a n=1
(±)-3.42b n=2

Scheme 10.

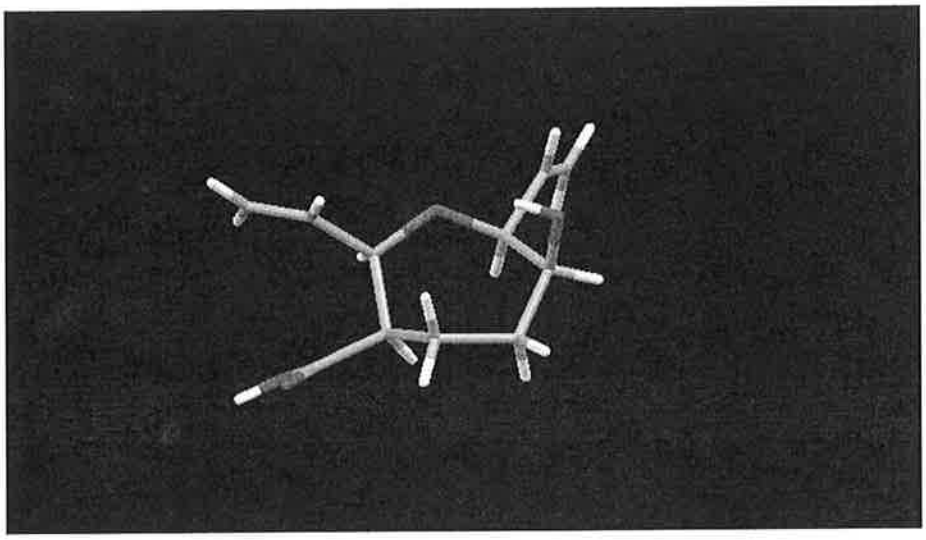
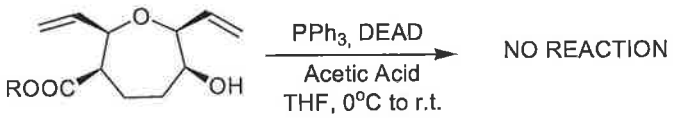


Figure 5. X-ray spectroscopy of compound **3.42a**.

The following step of the synthesis involved invertion of the configuration of the hydroxyl group in acid **3.42a.** Initially we tried the Mitsunobu reaction.[50]

When 1 mmol of **3.42a** was treated in presence of 5 mmol DEAD, 5 mmol PPh_3 and 5 mmol acetic acid in THF no reaction was observed (**Scheme 11**). This could be due, as reported in the literature[51], to the fact that the hydroxy acid under Mitsunobu conditions could undergo lactonization. However, in our case, only starting material was recovered.

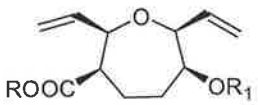


R= H **3.42a**
R= Me **3.43**

Scheme 11.

After this consideration the carboxylic acid of compound **3.42a** was protected as methyl ester **3.43** using 0.3 mmol of acetylchloride in MeOH. Subsequently, **3.43** was subjected to Mitsunobu conditions but only starting material was recovered (**Scheme 11**).[52] The failure of the Mitsunobu reaction moved our focus to other synthetic strategies.

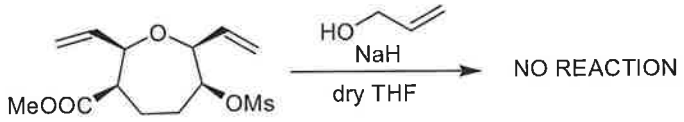
We treated the alcohol moiety of **3.42a** and **3.43** with MsCl, TsCl or $(Tf)_2O$ (**Table 2**) aiming to yield a better leaving group that can be used in a SN_2 reaction with the desired alkoxide. As reported in **Table 2**, entry 5, **3.43** reacted only in the presence of Methanesulfonylchloride and Et_3N in CH_2Cl_2 yielding **3.43e** in 61%. To compound **3.43e** dissolved in dry THF was added a solution of allylalcohol pretreated with NaH in dry THF, but unfortunately only starting material was recovered (**Scheme 12**).



3.43a-e

Entry	Compound	R	R_1	Yield
1	**3.43a**	H	TfO	Polymerization
2	**3.43b**	H	Ts	0%
3	**3.43c**	H	Ms	0%
4	**3.43b**	Me	TfO	Polymerization
5	**3.43e**	Me	Ms	61%

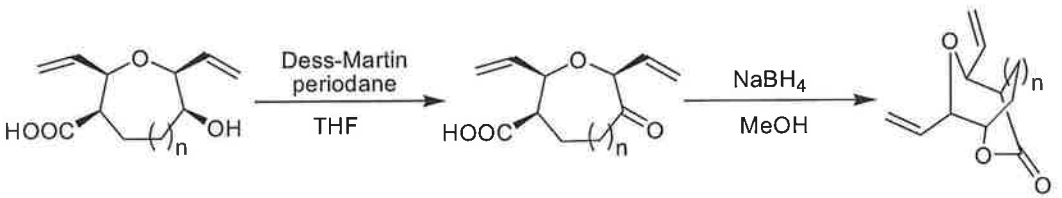
Table 2. Reaction of compounds **3.42a** and **3.43** with MsCl, TsCl or $(Tf)_2O$.



3.43e

Scheme 12.

We have also tried to invert the alcohol by oxidising it to the ketone and subsequently reducing it again using $NaBH_4$. This concept is based on the coordination between sodium and two oxygen atoms of the carboxylic acid and the ketone leaving only one face available for the H^- attack. Compounds **3.42a** and **3.42b** were reacted with 1.2 equiv of Dess-Martin periodane[53] in dry CH_2Cl_2 to afford **3.44a** in 54% yield and **3.44b** in 40% yield. The subsequent reduction of the ketone **3.44a** in presence of 1 equiv. of $NaBH_4$ in MeOH yield the lactone **3.41a** in 30% yield (**Scheme 13**).[54]



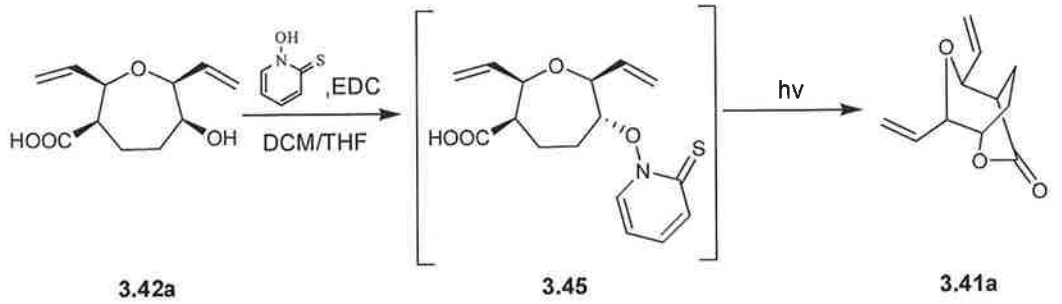
3.42a n=1
3.42b n=2

3.44a n=1
3.44b n=2

3.41a n=1

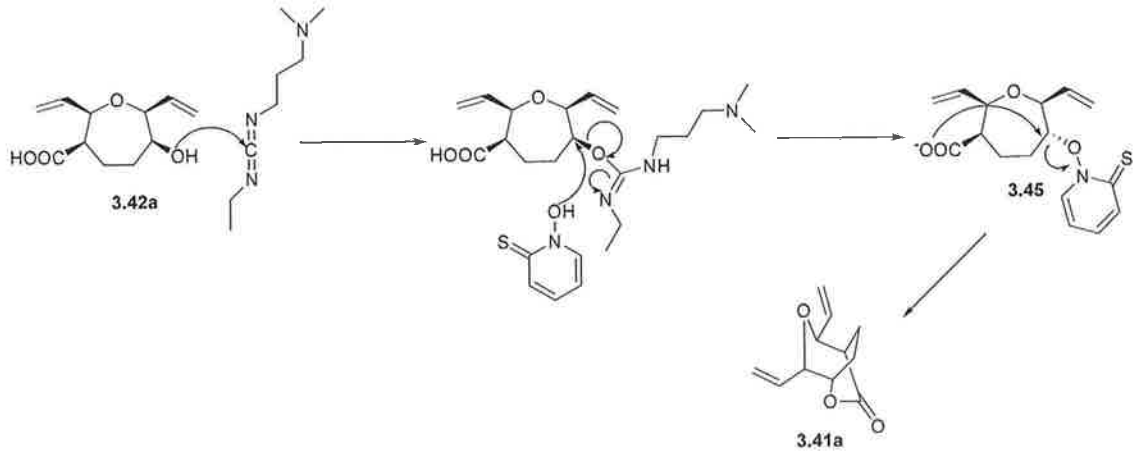
Scheme 13.

After these results we decided to focus our studies on the conversion of the carboxylic acid to an alcohol. Therefore compound **3.42a** was submitted to the Barton decarboxylation procedure.[55] **3.42a** was dissolved in THF and CH_2Cl_2 was reacted with 1.5 equiv of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and 1.5 equiv of 2-mercaptopyridine-N-oxide dissolved in CH_2Cl_2 in a dark environment to give the Barton ester intermediate **3.45**, which was irradiated with a 500W halogen lamp in the presence of Oxygen gas.[56]



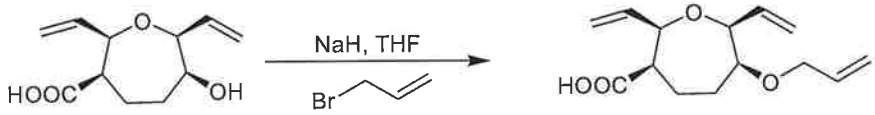
Scheme 14.

Instead of yielding the desired decarboxylated product, lactone **3.41a** was isolated. This result could be explained by the reaction between EDC and the secondary alcohol moiety of **3.46a** to obtain a good leaving group which reacts with 2-mercaptopyridine-N-oxide by a S_N2 mechanism to afford compound **3.45.** After ring closure of **3.45**, lactone **3.41a** was recovered (**Scheme 15**).



Scheme 15.

After this result the protection of the alcohol group of **3.42a** was necessary. Compound **3.46** was obtained in 65% yield from **3.42a** in the presence of allylbromide and NaH in THF (**Scheme 16**).

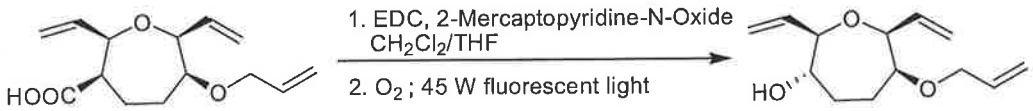


3.42a **3.46**

Scheme 16.

With compound **3.46** in our hands, the Barton decarboxylation was performed. **3.46** was reacted under Barton decarboxylation conditions to yield compound **3.47** only in 10% yield (**Scheme 17).**

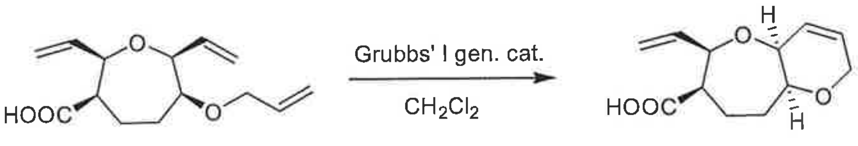
We decided to investigate the light intensity and type with the aim of improving the yield. When 60 W bulb was used only starting material was recovered, however with 75 W and 45W fluorescent lights the desired compound **3.47** was isolated respectively in 47% and 49% yields.



3.46 **3.47**

Scheme 17.

At the same time a ring closing metathesis (RCM) was performed on compound **3.46** was performed using 10 mol% Grubbs' I generation catalyst to yield compound **3.48** in 65% yield (**Scheme 18**). The RCM between the two alkenes in position 2 and 3 was obtained as desired.

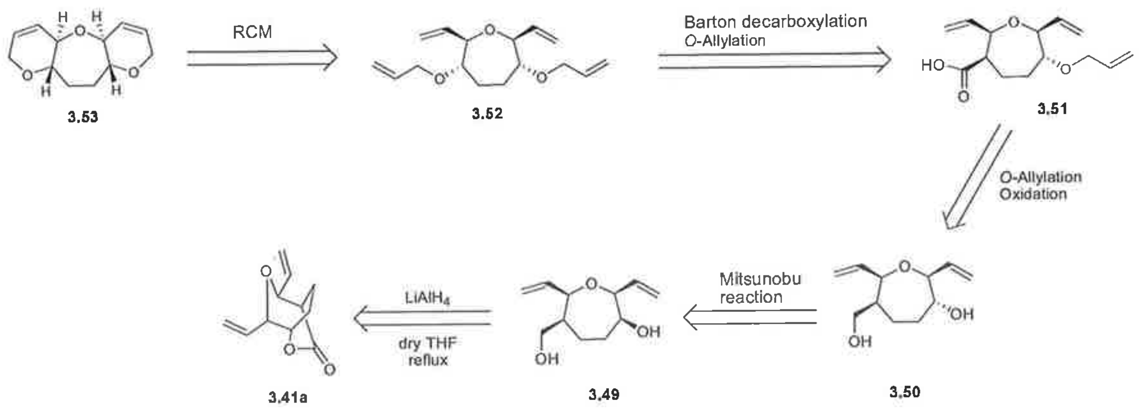


3.46 **3.48**

Scheme 18.

3.5 Future work.

With all this data in hand, we decided to investigate a suitable way to afford the inversion of the alcohol in compound **3.42a (Scheme 19**). In order to reduce the synthetic steps a good strategy could be to start from lactone **3.41a** which may undergone to ring opening to obtain compound **3.53** in 69% in the presence of 2 equiv. $LiAlH_4$.[57] The secondary alcohol of **3.49** can be inverted by a Mitsunobu reaction to give **3.50.** The next step will be oxidation of the primary alcohol to obtain a carboxylic acid moiety using TEMPO, KBr, $NaHCO_3$, NaOCl[58] and the protection of the secondary alcohol as allyl ether. Compound **3.51** may undergo Barton decarboxylation and subsequently allylation to give **3.52**. At the end the RCM will be performed to obtain the desired compound **3.53** containing three oxo rings in *trans* configuration.



Scheme 19.

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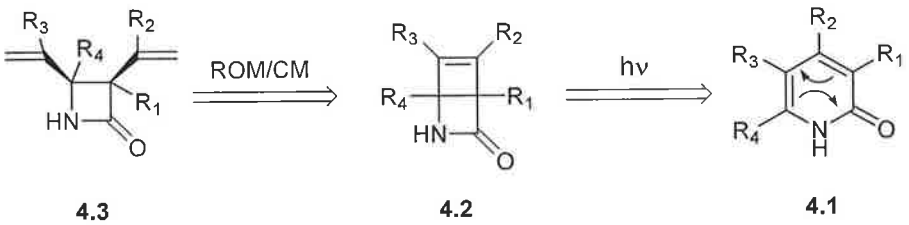
4.1 Aim

As part of our programme of research on the generation of chemical diversity by reacting aromatic heterocycles[1] possessing a low degree of aromaticity, we investigated a novel synthesis of monobactams starting from 2-pyridones **4.1(Scheme 1)**.



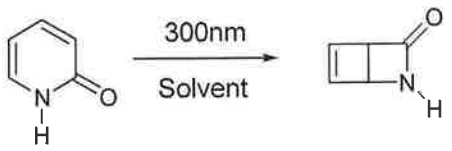
4.3 **4.2** **4.1**

Scheme 1.

Compounds **4.1** undergo photochemical electrocyclization, as reported,[2-3] to furnish bicyclic structures **4.2**. The cyclization is stereoselective and only *cis* fused bicyclic **4.2** was obtained. It was reasoned that if compounds **4.2** were metathesis active, their reaction with alkenes would furnish a novel method to produce monobactams **4.3**. Compounds **4.3** contain two alkene moieties that in turn could be employed to prepare libraries of monobactams for biological evaluation. As ring strain is the major driving force promoting ring opening metathesis (ROM)/cross metathesis (CM) sequences,[4] we were sufficiently confident in the viability of the reaction leading from **4.2** to **4.1** (**Scheme 1**). Importantly, in this synthesis, variation of the alkene component in the ROM/CM step or introduction of a substituent in the pyridone substrate would furnish an efficient means to generate libraries of compounds.

4.2 Results and Discussion

Herein we present an extension of this study in which the title compound **4.1** were used for the development of a new monobactam synthesis. With the aim of obtaining compound **4.2a-e** in sufficient amounts for preparative studies, we investigated the reaction of 2-pyridones **4.1a-e** in several solvents and concentrations using a 300nm light. 2-Hydroxypyridone dissolved in dry THF (10^{-3}M) afforded the corresponding bicyclic product **4.2a** in 48% yield in 37 h. (**Table 1**, entry 5). Using CH_3CN as solvent the yields were measured as 50% (**Table 1**, entries 1, 2 and 4) and increasing the pyridone concentration to 10^{-1}M allowed isolating compound **4.2a** in only 6% yield after purification on neutral alumina.



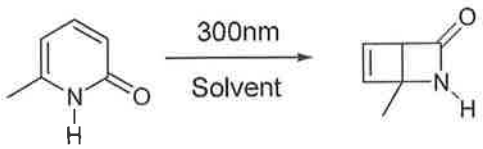
4.1a **4.2a**

Entry	Solvent	[M]	Time [h]	Yield [%]
1	CH_3CN	10^{-3}	72	50[a]
2	CH_3CN	10^{-3}	96	40[a]
3	CH_3CN	10^{-1}	192	6[a]
4	CH_3CN dry	10^{-2}	48	50[a]
5	THF dry	10^{-3}	39	48[a]

[a]Purification by neutral alumina

Table 1. Screening of 2-hydroxypyridone to photochemical induced electrocyclisation.

While electrocyclisation of unsubstituted pyridone worked reasonably well, electrocyclisation of 6-methyl-2-hydroxy-pyridone **4.1b** was problematic and degradation of the starting material was observed under several conditions (**Table 2**, entries 1-8); the only exception was represented by DCM as solvent (**Table 2**, entries 9), in which case the starting material **4.1b** was recovered, although quantitative conversions of **4.1b** were often reported.[5]



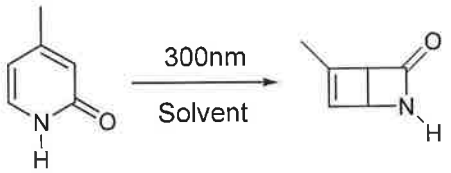
4.1b **4.2b**

Entry	Solvent	[M]	Time [h]	Yield [%]
1	CH_3CN	10^{-3}	72	Degradation
2	EtOAc	10^{-3}	93	Degradation
3	EtOAc	10^{-3}	21	Degradation
4	EtOAc dry	10^{-4}	72	Degradation
5	EtOAc dry	10^{-2}	15	Degradation

6	THF dry	10^{-3}	72	Degradation
7	THF dry	10^{-3}	55	Degradation
8	THF dry	10^{-3}	40	Degradation
9	CH_2Cl_2	10^{-3}	150	-

Table 2. Screening of 6-methyl-2-hydroxy-pyridone to photochemical induced electrocyclisation.

On the contrary, 4-methyl-2-hydroxypyridone **4.1c** reacted in EtOAc to furnish after two hours compound **4.2c** in 75% yield (**Table 3**, entry 1); increasing of the reaction time to 15h decreased the yield to only 32% after isolation on silica gel (**Table 3**, entry 2). The isolation media proved to be crucial to obtain higher yields. After deposition of crude product on silica gel, several additional side products were observed. When **4.1c** was used at the concentration of 10^{-2}M (**Table 3**, entry 3) or in other type of solvents such as CH_3CN and THF degradation of starting material was observed.



4.1c **4.2c**

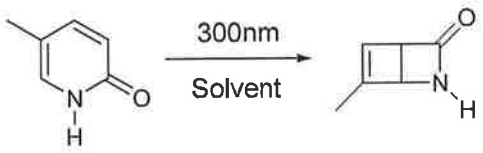
Entry	Solvent	[M]	Time [h]	Yield [%]
1	EtOAc	10^{-3}	2	75[a]
2	EtOAc dry	10^{-3}	15	32[b]
3	EtOAc dry	10^{-2}	1	Degradation
4	CH_3CN dry	10^{-2}	15	Degradation
5	THF dry	10^{-3}	20	Degradation
6	THF dry	10^{-2}	10	Degradation

[a]Purification by neutral alumina; [b]Purification by silica gel.

Table 3. Screening of 4-methyl-2-hydroxy-pyridone to photochemical induced electrocyclisation.

We then studied the photochemistry of 5-methyl-2-hydroxypyridone **4.1d** by dissolving this in EtOH (10^{-3}M) and irradiation by 300nm light; under these conditions the corresponding bicyclic **4.2d** was obtained in 70% yield after purification by neutral alumina (**Table 4**, entry 3). Using other

solvents such as EtOAc (**Table 4**, entry 1) or THF (**Table 4**, entry 2) compound **4.2d** was isolated in 30% and 25% yield respectively after purification by silica gel.



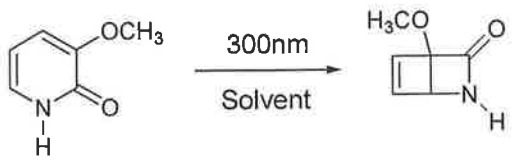
4.1d **4.2d**

Entry	Solvent	[M]	Time [h]	Yield [%]
1	EtOAc	10^{-3}	15	30[b]
2	THF	10^{-3}	20	25[b]
3	EtOH	10^{-3}	20	70[a]

[a]Purification by neutral alumina; [b]Purification by silica gel.

Table 4. Screening of 5-methyl-2-hydroxy-pyridone to photochemical induced electrocyclisation.

3-Methoxy-2-hydroxypyridone **4.1e** dissolved in CH_3CN gave compound **4.2e** in 25% yield (**Table 5**, entry 3); replacement of CH_3CN with EtOAc or THF gave a large number of degradation products (**Table 5**, entries 1 and 2).



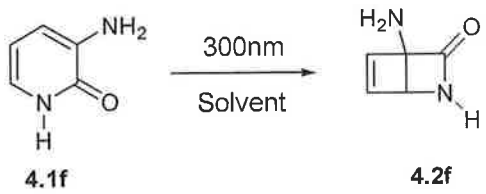
4.1e **4.2e**

Entry	Solvent	[M]	Time [h]	Yield [%]
1	EtOAc	10^{-3}	24	Degradation
2	THF	10^{-3}	24	Degradation
3	CH_3CN	10^{-3}	24	25[a]

[a]Purification by silica gel.

Table 5. Screening of 3-methoxy-2-hydroxypyridone to photochemical induced electrocyclisation.

We have also studied the photochemistry of 3-amino-2-pyridinol **4.1f** without any good result; in this case only degradation of starting material was observed (**Table 6**, entrie 1-3) with no evidence for the formation of desired **4.2f**.



4.1f **4.2f**

Entry	Solvent	[M]	Time [h]	Yield [%]
1	EtOAc	10^{-3}	15	Degradation
2	THF	10^{-3}	15	Degradation
3	CH_3CN	10^{-3}	15	Degradation

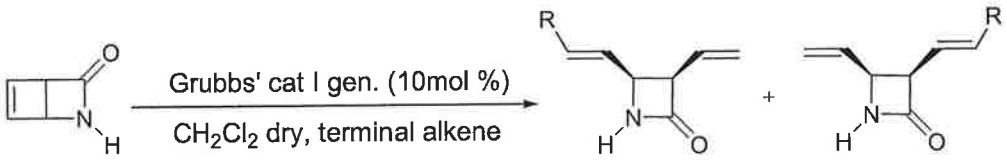
Table 6. Screening of 3-amino-2-pyridinol to photochemical induced electrocyclisation.

With these results in hand we investigated the ROM/CM of compound **4.2a**, **4.2c** and **4.2d**, which were selected as examples of unsubstituted and substituted cyclobutenes.

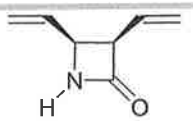
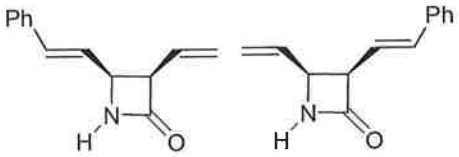
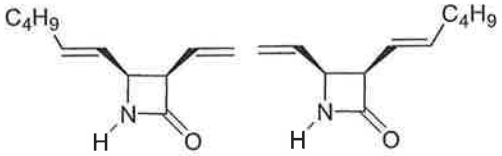
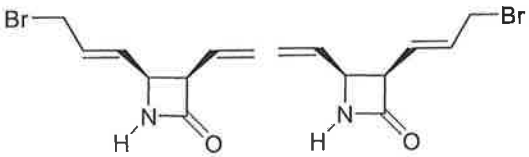
The reactions were performed using Grubbs' catalyst I generation, II generation and Grubbs'-Hoveyda II generation, but the only good results were obtained using Grubbs' I generation.

Initially, Grubbs' catalyst I was added in one portion at the onset of the reaction. Later it was found that cleaner and higher yielding reactions were obtained by dropwise addition of a freshly prepared solution of the ruthenium catalyst in dichloromethane.

First **4.2a** was reacted with ethylene in presence of 10 mol% of Grubbs' cat I gen. to give the desired compound **4.3** in 50% yield with recovery of starting material (**Table 7**, entry 1). Addition of further amounts of ethylene did not improve the yield. The reaction proceeded to full conversion after addition of a further 10 mol% of Grubbs' catalyst to the reaction mixture, giving compound **4.3** in 82% yield. Increasing the temperature did not allow improvement the yield. When styrene or 1-hexene were used the expected two regioisomers **4.4**, **4.5**, **4.6**, **4.7** were obtained in very low yield (**Table 7**, entries 2 and 3). Using allylbromide as alkene no metathesis product was observed (**Table 7**, entry 4).



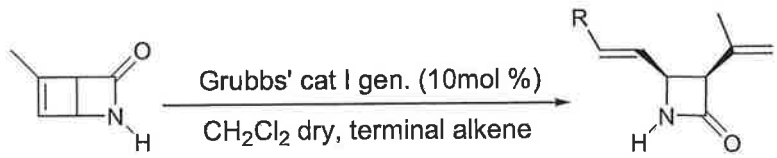
4.2a **4.3-4.9**

Entry	Alkene	Product	Yield [%][b]
1	Ethylene	 **4.3**	50
2	Styrene	 **4.4** **4.5**	(4) (4)
3	1-Hexene	 **4.6** **4.7**	(3) (1)
4	Allylbromide	 **4.8** **4.9**	-

[a]Conditions: bicyclic compounds **4.2a** (1 mmol.), cat. (10 → 20 mol %), dry CH_2Cl_2 (14 mL), alkene: styrene (5 mmol); 1-hexene (5 mmol); allylbromide (5 mmol); ethylene under pressure (300 psi), r.t.; [b] Isolated yields after column chromatography.

Table 7. ROM/CM of compound **4.2a**.

Results collected using **4.2c** matched those for **4.2a**. When ethylene was used as the alkene under pressure (300 psi) the desired open product **4.10** was obtain in 28% yield (**Table 8**, entry 1) and in 75% when other 10 mol% of Grubbs' catalyst was added. Using styrene and 1-hexene compounds **4.11** and **4.12** were isolated as only one regioisomer in 15% and 10% yield respectively (**Table 8**, entries 2 and 3).



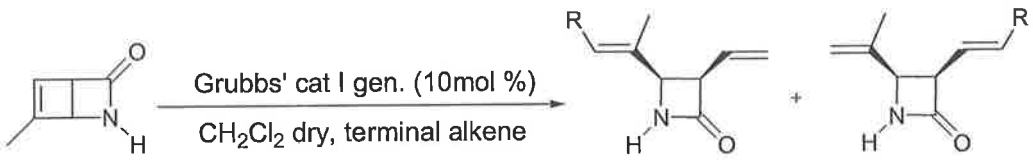
4.2c **4.10-4.12**

Entry	Alkene	Product	Yield [%]
1	Ethylene	**4.10**	28[c]
2	Styrene	**4.11**	15[d]
3	1-Hexene	**4.12**	10

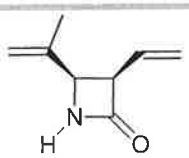
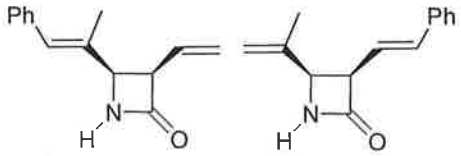
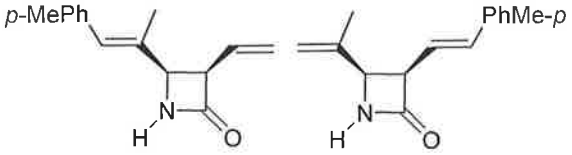
[a]Conditions: bicyclic compounds **4.2c** (1 mmol.), cat. (10 → 20 mol %), dry CH_2Cl_2 (14 mL), alkene: styrene (5 mmol); 1-hexene (5 mmol); ethylene under pressure (300 psi), r.t.; [b]Isolated yields after column chromatography; [c]When the reaction was performed at -78°C no ROM/CM product was observed; [d]When dry THF was used as solvent instead of dry CH_2Cl_2 no product was observed.

Table 8. ROM/CM of compound **4.2c**.

When compound **4.2d** was submitted to ROM/CM conditions none of the expected products was observed and only starting material was recovered (**Table 9**, entries 1-3).



4.2d **4.13-4.17**

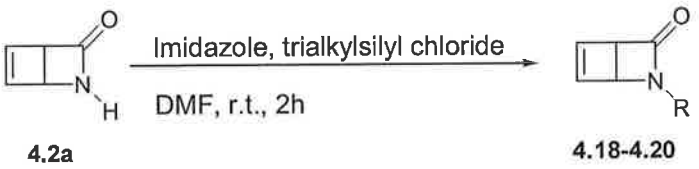
Entry	Alkene	Product	Yield [%]
1	Ethylene	 **4.13**	-
2	Styrene	 **4.14** **4.15**	-
3	*p*-Me-Styrene	 **4.16** **4.17**	-

[a]Conditions: bicyclic compounds **4.2d** (1 mmol.), cat. (10 → 20mol %), dry CH_2Cl_2 (14 mL), alkene: styrene (5 mmol); *p*-Me-styrene (5 mmol); ethylene under pressure (300 psi), r.t.; [b]Isolated yields after column chromatography.

Table 9. ROM/CM of compound **4.2d**.

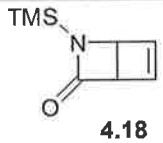
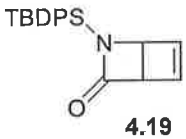
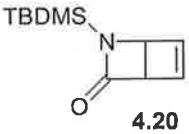
The following observations suggested that incomplete conversion in the experiments employing 10 mol % of catalyst can be attributed to the deactivation of the metathesis catalyst: *(a)* the 2-azetidinone ring impedes delocalisation of the nitrogen lone pair, hence this could act as a ligand. *(b)* During the purification of compounds **4.3-4.12**, a discrete compound was repeatedly obtained containing monobactam and ruthenium; as yet we have not established the structure of this compound. *(c)* Free cyclohexylphosphine was obtained in the crude reaction mixture, indicating displacement of this ligand from the metal.[6]

In order to obviate to this problem, we decided to protect the nitrogen in compounds **4.2a** and **4.2c**. Different silicon based protecting groups were employed. First compound **4.2c** was reacted with 2 eq. of TMSCl in presence of 1.1 eq. imidazole as base in DMF at r.t. (**Table 10**, entry 1) to give **4.18** in 10% yield. Following the same procedure but using TBDPSCl and TBDMSCl the yield of the corresponding protected compounds **4.19** and **4.20** were 37% and 63% respectively (**Table 10**, entries 2 and 3).



4.2a **4.18-4.20**

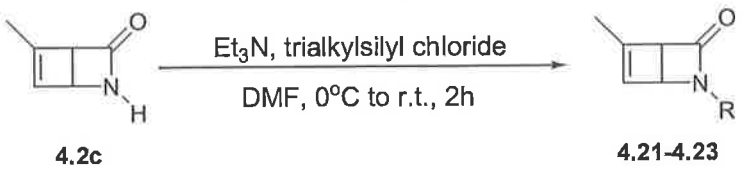
R= TMS, TBDP, TBDM

Entry	Substrate	Reactant	Product	Yield [%][a]
1	**4.2a**	TMSCl	 **4.18**	10
2	**4.2a**	TBDPSCl	 **4.19**	37
3	**4.2a**	TBDMSCl	 **4.20**	63

[a]Isolated yield after column chromatography.

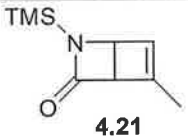
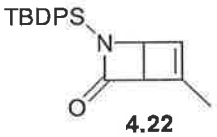
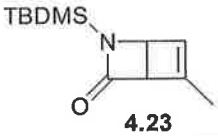
Table 10. Protection of photoisomers **4.2a**.

When compound **4.2c** underwent the same conditions studied for compound **4.2a** the corresponding TMS-protected compound **4.21** was obtained in 9% yield (**Table 11,** entry 1). After this negative result we decided to change the base employed. When 1.2 eq. of Et_3N was used at r.t. **4.21** was isolated in 18% yield, reducing the temperature to 0°C during the addition of the base the desired compound **4.21** was obtained in 51% yield. Following this procedure and employing TBDPSCl and TBDMSCl as protecting group the corresponding products **4.22** and **4.23** were obtained in 28% and 90% yield respectively (**Table 11,** entries 2 and 3).[1c]



4.2c **4.21-4.23**

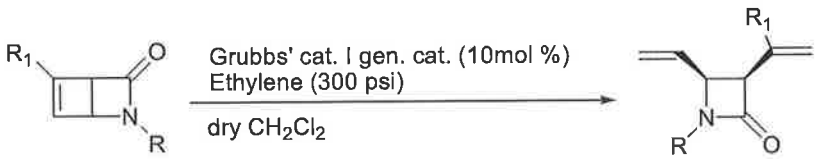
R= TMS, TBDP, TBDM

Entry	Substrate	Reactant	Product	Yield [%][a]
1	4.2c	TMSCl	 4.21	51
2	4.2c	TBDPSCl	 4.22	28
3	4.2c	TBDMSCl	 4.23	90

[a]Isolated yield after column chromatography.

Table 11. Protection of photoisomers **4.2c**.

At this point we investigated the ROM/CM on the silyl protected β-lactames **4.18-4.23**. 10 mol % of Grubbs' catalyst I generation dissolved in DCM was used in presence of ethylene under pressure (300psi). Reaction of compounds *N*-TMS **4.21** and **4.18** gave a complex reaction mixture (**Table 12**, entries 1 and 4). When compound **4.19** and **4.22** underwent ROM/CM condition they gave the desired alkenes **4.25** and **4.28** in 57% and 53% yield respectively (**Table 12**, entries 2 and 5). The best results were obtained when the bicyclic compounds **4.20** and **4.23** were employed to give the expected ring opening products **4.26** and **4.29** in 85% and 90% yield (**Table 12**, entries 3 and 6).

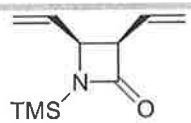


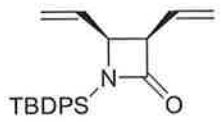
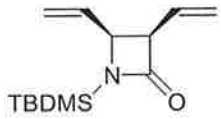
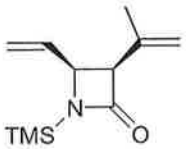
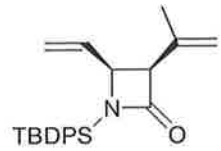
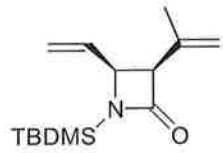
4.18-4.23

R= TMS, TBDP, TBDM

R_1= H, CH_3

4.24-4.29

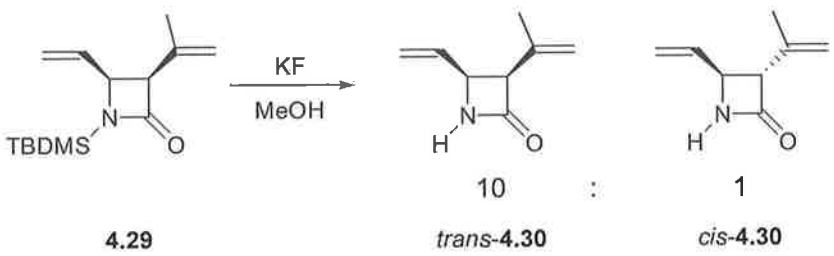
Entry	Substrate	Product	Yield [%][b]
1	4.18	 4.24	-

2	**4.19**	 **4.25**	57
3	**4.20**	 **4.26**	85
4	**4.21**	 **4.27**	-
5	**4.22**	 **4.28**	53
6	**4.23**	 **4.29**	90

[a]Conditions: bicyclic compounds **4.18-4.23** (1 mmol.), Grubbs' I generation catalyst (10 mol %), dry CH_2Cl_2 (14 mL), ethylene under pressure (300 psi); [b] Isolated yields after column chromatography.

Table 12. ROM/CM of compounds **4.18-4.23** with ethylene.

At this point the TBDMS group was removed in compound **4.29** by reaction with KF (1.1 equiv) in MeOH at -20 °C to give monobactam **4.30** in 83% yields. The cleavage of the silicon protecting group was accompanied by partial isomerisation, resulting in formation of 8% of the more stable *trans*-**4.30** which was isolated and fully characterised (**Scheme 2**).



4.29 *trans*-**4.30** *cis*-**4.30**

Scheme 2.

4.4 Conclusions

In conclusion, we have developed a novel route to alkene-functionalised monobactams. The synthesis made use of commercially available 2-pyridones and alkenes and furnished stereo-defined monobactams in high yields. The methodology presented is modular in nature and allows introduction of diversity by variation of one component at a time. Studies on the use of compound **4.30** in diversity oriented synthesis and for the preparation of unnatural α-amino acids are in progress.

4.5 References

[1] a) M. F. A. Adamo, E. F. Duffy *Org. Lett.* **2006**, *8*, 5157; b) M. F. A. Adamo, V. R. Konda *Org. Lett.* **2007**, *9*, 303; c) M. F. A. Adamo, E. F. Duffy, D. Donati, P. Sarti–Fantoni *Tetrahedron* **2007**, *63*, 2047; d) M. F. A. Adamo, E. F. Duffy, D. Donati, P. Sarti–Fantoni *Tetrahedron* **2007**, *63*, 2684; e) M. F. A. Adamo, V. R. Konda, D. Donati, P. Sarti–Fantoni, T. Torroba *Tetrahedron* **2007**, *63*, 9741; f) M. F. A. Adamo, M. Nagabelli *Tetrahedron Lett.* **2007**, *48*, 4703; g) M. F. A Adamo., V. R. Konda *Tetrahedron Lett.* **2008**, *49*, 6224; h) M. F. A. Adamo, S. Bruschi, S. Suresh, L. Piras *Tetrahedron Lett.* **2008**, *49*, 7406.

[2]a) R. Matzushima, K. Terada *J. Chem. Soc., Perkin Trans. 2* **1985**, 1445; b) T. Bach, H. Bergmann, K. Harms *Org. Lett.* **2001**, *3*, 601.

[3]J. Kurita, T. Yoneda, N. Kakusawa, T. Tsuchiya *Chem. Pharm. Bull.* **1990**, *38*, 2911.

[4]Grela, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 5504.

[5]a) R. Matzushima, K. Terada *J. Chem. Soc., Perkin Trans. 2* **1985**, 1445; b) T. Bach, H. Bergmann, K. Harms *Org. Lett.* **2001**, *3*, 601.

[6]S. J. P'Pool, H.-J. Schanz *J. Am. Chem. Soc.* **2007**, *129*, 14200.

Materials and Methods for Chapter 2.

General Methods. ^{1}H, ^{13}C, NMR spectra were recorded on a Varian AS 300, Bruker 400 and 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR (^{1}H NMR: 7.26 ppm for $CDCl_3$; ^{13}C NMR: 77.0 ppm for $CDCl_3$. ^{13}C NMR spectra were acquired with ^{1}H broad band decoupled mode. DMSO-d6 (referenced to 2.52 and 3.35 ppm for ^{1}H and 40.0 for ^{13}C). Coupling constants (*J*) are in Hz. Multiplicities are reported as follows: s, singlet, d, doublet, dd, doublets of doublets, t, triplet, q, quartet, m, multiplet, c, complex, and br, broad. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H), using a UV detector operating at 254 nm and 210nm. Melting points were determined using a Stuart scientific melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded as KBr discs using a Bruker Tensor27 FT-IR instrument. Absorption maximum (νmax) was reported in wave numbers (cm^{-1}) and only selected peaks are reported. High resolution mass spectra were obtained on a Waters Micro mass LCT and low resolution mass spectra were recorded on Waters Micro mass Quattro LCMS spectrometers at 70 eV. Tetrahydrofuran was freshly distilled over sodium benzophenone prior to use according to standard procedure. All other reagents and solvents were used as purchased from Aldrich. Reactions were checked for completion by TLC (EM Science, silica gel 60 F254). Flash chromatography was performed using silica gel 60 (0.040-0.063 mm, 230-400 mesh).

The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD, Chiracel OJ, Chiracel OD, Chiralpak AS columns), using a UV detector operating at 254 nm. Retention factors (Rf) are reported to ±0.05.

Racemic samples were prepared using tetra-*n*-butylammonium bromide as a catalyst at room temperature overnight. 3-Methyl-4-nitro-styrylisoxazoles were prepared through the Knoevenagel condensation between 3,5-dimethyl-4-nitroisoxazole and the appropriate aromatic or heteroaromatic aldehyde (piperidine 0.1 equiv., EtOH, 65 °C, 2-3 hours).

2.1 Experimental Details for Chapter 2.

General procedure for the organocatalytic, enantioselective Michael addition of ethylisocyanoacetate to 5-styrylisoxazoles 2.17a-n.

To a test tube equipped with a magnetic stirring bar were sequentially added the 5-styrylisoxazole **2.17a-n** (0.1 mmol), catalyst **2.39** or **2.38** (10 mol%), ethylisocyanoacetate (0.5 mmol) and toluene (0.5 mL). The test tube was placed at -20°C, then finely ground K_2CO_3 (0.5 mmol) was added in one portion. The mixture was then vigorously stirred at the same temperature, with no precautions to exclude moisture or air. After the stated reaction time, the reaction was filtered on a short plug of silica gel to remove the catalyst, the solvents evaporated using a water bath at 50°C to remove ethylisocyanoacetate in excess, and the residue eventually analysed by means of ^{1}H NMR spectroscopy to determine the diastereomeric ratio and the conversion.

General procedure for the cyclic products 2.20a-n and 2.42a-b.

To a solution of **2.19a-n** or **2.41a-b**(0.1 mmol) in THF (1.0 mL) at 45°C, DIPEA (0.2 mmol) was added. The solution was stirred until the starting material was consumed.
The solvents were removed under reduced pressure and the residue purified by silica gel chromatography.

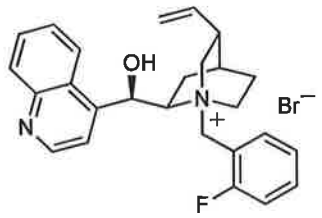
The following catalysts were commercially available: **2.21**, **2.22**, **2.23** and **2.24**.
The following were prepared using literature procedure: **2.26**[1], **2.32**[2].
The following were already present in Adamo's laboratory: **2.25**, **2.27**, **2.30**, **2.36**, **2.37**.

General procedure for the catalysts 2.28, 2.29, 2.31, 2.33, 2.34, 2.35.

To a stirred suspension of cinchonidine (1.0 mmol) in THF (3.0 mL), the corresponding benzyl bromide (1.3 mmol) was added. The resulting mixture was then heated at 60°C, and stirred for 36h at the same temperature. After cooling to rt, the precipitate was

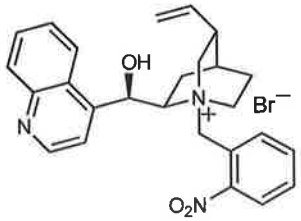
collected by Bückner filtration and washed several times with Et_2O, affording the title compound.

_N_-(2-Fluorobenzyl)cinchonidinium bromide (2.28).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, J =4.6 Hz, 1H), 8.32 (d, J = 7.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.93-7.76 (m, 5H), 7.43 (t, J = 8.8 Hz, 2H), 6.82-6.73 (m, 1H), 6.52 (bs, 1H), 6.08-5.96 (m, 1H), 5.33-5.16 (m, 2H), 5.12-4.98 (m, 1H), 4.89-4.79 (m, 1H), 4.25-4.17 (m, 1H), 3.91 (t, J = 9.5 Hz, 2H), 3.46 (t, J = 11.4 Hz, 1H), 2.95 (dd, J = 20.9, 10.0 Hz, 1H), 2.69-2.61 (m, 1H), 2.44-2.31 (m, 1H), 1.91 (bs, 1H), 1.86-1.73 (m, 2H), 1.24-1.11 (m, 1H).

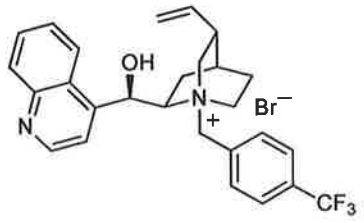
_N_-(2-Nitrobenzyl)cinchonidinium bromide (2.29).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, J =4.6 Hz, 1H), 8.37 (d, J = 7.8 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.17-8.09 (m, 2H), 8.06-7.82 (m, 5H), 6.88-6.66 (m, 1H), 6.10-5.96 (m, 1H), 5.96-5.85 (m, 1H), 5.56-5.34 (m, 1H), 5.35-5.21 (m, 2H), 4.49-4.38 (m, 1H), 4.18 (t, J = 9.3 Hz, 1H), 4.22-3.98 (m, 1H), 3.55-3.28 (m, 1H), 3.20 (dd, J = 20.9, 9.2 Hz, 1H), 2.75 (dd, J = 17.2, 8.5 Hz, 1H), 2.61-2.45 (m, 1H), 1.95 (bs, 1H), 1.98-1.75 (m, 2H),

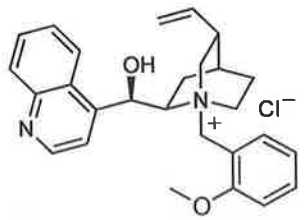
1.17-1.00 (m, 1H).

N-(4-Trifluoromethylbenzyl)cinchonidinium bromide (2.31).



1H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 4.4 Hz, 1H), 8.34 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 4.2 Hz, 1H), 7.86-7.76 (m, 2H), 7.56 (d, J = 8.3Hz, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.01 (t, J = 7.4 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.69-6.56 (m, 1H), 6.53-6.34 (m, 2H), 5.94-5.76 (m, 1H), 5.49-5.31 (m, 1H), 5.24 (d, J = 10.4 Hz, 1H), 5.21 (d, J = 17.4 Hz, 1H), 4.61-4.39 (m, 1H), 4.32-4.07 (m, 2H), 3.21 (t, J = 11.4 Hz, 1H), 2.71-2.61 (m, 1H), 2.34-2.16 (m, 1H), 2.36-2.12 (m, 1H), 1.86 (bs, 1H), 1.82-1.69 (m, 2H), 0.81-0.64 (m, 1H).

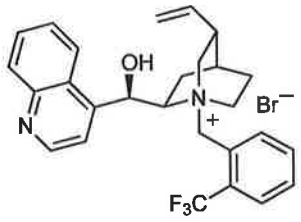
N-(2-Methoxylbenzyl)cinchonidinium bromide (2.33).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J =4.2 Hz, 1H), 8.28 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 4.1 Hz, 1H), 7.60 – 7.42 (m, 3H), 7.05-6.94 (m, 2H), 6.65-6.53 (m, 3H), 6.49 (bs, 1H), 6.14-5.99 (m, 1H), 5.88-5.75 (m, 1H), 5.40-5.25 (m, 1H), 5.25-5.09 (m, 2H), 4.46-4.34 (m, 1H), 4.20-3.99 (m, 2H), 3.79 (s, 3H), 3.26 (t, J = 11.5 Hz, 1H), 2.73 (dd, J =

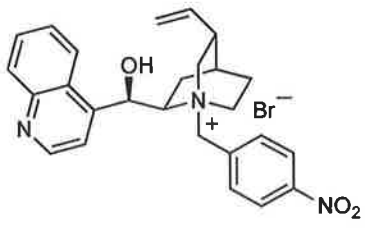
21.0, 10.1 Hz, 1H), 2.26 (dd, J = 17.0, 8.6 Hz, 1H), 2.11-2.00 (m, 1H), 1.76 (bs, 1H), 1.73-1.59 (m, 2H), 0.74-0.62 (m, 1H).

N-(2-Trifluoromethylbenzyl)cinchonidinium bromide (2.34).



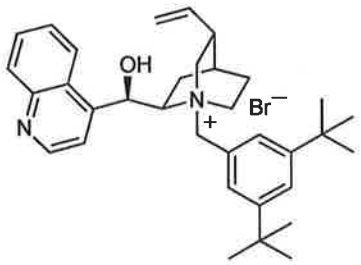
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, J = 4.8 Hz, 1H), 8.57-8.44 (m, 1H), 8.24-8.13 (m, 2H), 8.08 (d, J = 7.8 Hz, 1H), 8.02-7.88 (m, 5H), 6.77-6.59 (m, 1H), 6.15-6.06 (m, 1H), 5.44-5.03 (m, 4H), 4.66-4.40 (m, 1H), 4.11-3.99 (m, 2H), 3.63 (t, J = 11.4 Hz, 1H), 3.18-2.99 (m, 1H), 2.71-2.59 (m, 1H), 2.56-2.43 (m, 1H), 2.02-1.93 (m, 1H), 1.93-1.75 (m, 2H), 1.21-1.08 (m, 1H).

N-(4-Nitrobenzyl)cinchonidinium bromide (2.35).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (d, J =4.2 Hz, 1H), 8.25 (d, J = 7.8 Hz, 1H), 7.98-7.92 (m, 4H), 7.87 (d, J = 4.2 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.07 – 6.93 (m, 2H), 6.54-6.34 (m, 3H), 5.91-5.73 (m, 1H), 5.73-5.57 (m, 1H), 5.31-5.15 (m, 2H), 4.62-4.49 (m, 1H), 4.32-4.06 (m, 2H), 3.15 (t, J = 11.3 Hz, 1H), 2.82-2.63 (m, 1H), 2.42-2.27 (m, 1H), 2.21-2.04 (m, 1H), 1.83 (s, 1H), 1.80-1.74 (m, 2H), 0.81-0.69 (m, 1H).

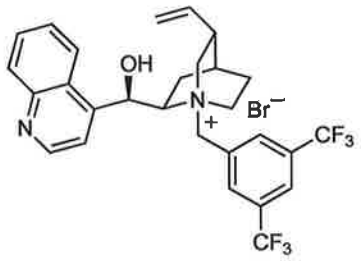
_N_-3,5-Bis(*tert*-butylbenzyl)cinchonidinium bromide (2.38).



To a stirred suspension of cinchonidine (1.0 mmol) in THF (3.0 mL), 3,5-bis(*tert*-butyl)benzyl bromide (1.3 mmol) was added. The resulting mixture was then heated at 60°C, and stirred for 36h at the same temperature. After cooling to rt, the precipitate was collected by Bückner filtration and washed several times with Et_2O, affording the title compound as a white solid in 80% yield.

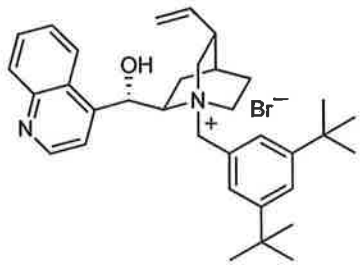
$[\alpha]_D^{25}$ = -105.5 (c = 0.80, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (d, J= 4.4, 1H), 8.12-8.10 (m, 1H), 7.98 (d, J= 8, 1H), 7.82-7.81 (m, 1H), 7.69 (d, J= 1.6, 2H), 7.66-7.58 (m, 2H), 7.51 (s, 1H), 6.76-6.68 (m, 2H), 5.90-5.87 (m, 1H), 5.60-5.52 (m, 1H), 5.13-5.09 (m, 2H), 5.02 (d, J= 10.4, 1H), 4.92-4.88 (b, 1H), 3.79 (t, J= 8.4, 1H), 3.68-3.62 (m, 1H), 3.49-3.43 (b, 1H), 3.33-3.31 (b, 1H), 2.63 (b, 1H), 2.17-2.12 (b, 2H), 1.99 (s, 1H), 1.67 (b, 1H), 1.33 (s, 18H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 152.2, 149.5, 147.2, 145.9, 136.5, 129.8, 129.6, 128.3, 127.9, 126.3, 124.8, 124.4, 123.0, 120.2, 117.9, 68.5, 64.6, 63.8, 61.3, 51.6, 38.0, 35.1, 31.47, 26.7, 24.9, 21.7.

N-(3,5-bis(trifluoromethyl)benzyl) cinchonidinium bromide (2.39).



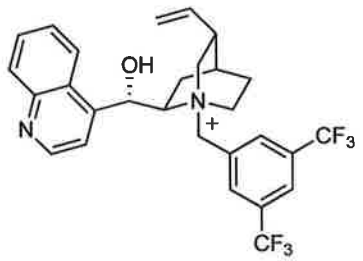
To a stirred suspension of cinchonidine (1.0 mmol) in THF (3.0 mL), 3,5-bis(trifluoromethyl)benzyl bromide (1.3 mmol) was added. Following the procedure used for **2.38**, the title compound was obtained as a brown solid in 70% yield.
Spectral data were consistent with the literature.[3]

N-3,5-Bis(*tert*-butylbenzyl)cinchonium bromide (2.38').



Following the procedure used for **2.38**, the title compound was obtained as a white solid in 80% yield.
Spectral data were consistent with the literature.[4]

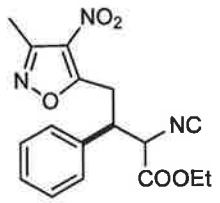
N-(3,5-bis(trifluoromethyl)benzyl) cinchonium bromide (2.39').



Following the procedure used for **2.39**, the title compound was obtained as a white solid in 78% yield.

Spectral data were consistent with the literature.[5]

(3*R*)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylbutanoate (2.19a).

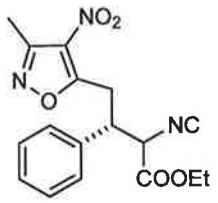


Following the general procedure using ethylisocyanoacetate and catalyst **2.39** (6 mg, 0.010 mmol, 10 mol%) for 78h at -20° C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) dried and the title compound was obtained in 81% yield (dr 1:1) as a yellow oil.

IR 2985, 2148, 1754, 1520; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.27 (m,10H), 4.64 (d, J= 4.5, 1H), 4.52 (t, J= 2.4, 1H), 4.26-4.19 (dq, J= 7.2, J= 14.4, 2H), 4.17-4.10 (dq, J= 6.9, J= 14.1, 2H), 4.02-3.90 (m, 4H), 3.78-3.65 (m, 2H), 2.52 (s, 3H), 2.48 (s, 3H), 1.24 (t, J= 7.2, 3H), 1.51 (t, J=7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.3, 171.2, 164.9, 164.6, 163.6, 163.2, 155.8, 155.6, 135.9, 134.8, 129.2, 129.0, 128.9, 128.9, 128.1, 127.7, 63.3,

63.0, 61.8, 61.0, 44.8, 44.1, 30.2, 28.6, 14.0, 13.9, 11.6, 11.6. HRMS found:$[M-H]^-$ 342.0918, $C_{17}H_{16}N_3O_5$, requires: 342.1090; m/z: 342 (100%, $[M-H]^-$).

(3*S*)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylbutanoate (*ent*-2.19a).



Following the general procedure using ethylisocyanoacetate and catalyst **2.39'** (6 mg, 0.010 mmol, 10 mol%) for 78h at -20° C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 79% yield (dr 1:1) as yellow oil.

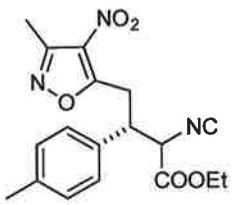
Spectral data were identical to compound **2.19a**.

(3*R*)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-*p*-tolylbutanoate (2.19b).

Following the general procedure using ethylisocyanoacetate and catalyst **2.39** (6.0 mg, 0.010 mmol, 10 mol%) for 52 h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 81% yield (dr 1:1) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (d, J=8, 4H), 7.05 (d, J=7.6, 4H), 4.52 (d, J= 4.4, 1H), 4.40 (d, J= 3.2, 1H), 4.40-4.09 (m, 2H), 4.06 (dq, J= 7.2, J= 14.4, 2H), 3.9-3.81 (m, 4H), 3.65-3.57 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 2.24 (s, 6H), 1.17 (t, J= 7.2, 3H), 1.09 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.44 , 171.3, 165.0, 164.6, 155.7, 155.6, 138.8, 138.7, 132.7, 131.6, 129.8, 129.6, 127.9, 127.5, 63.3, 63.0, 62.0, 61.0, 44.4, 43.8, 30.3, 28.6, 21.1, 21.1, 13.9, 11.6, 11.6. HRMS found:$[M-H]^-$ 356.1255, $C_{18}H_{18}N_3O_5$, requires: 356.1246; m/z: 356 (100%, $[M-H]^-$).

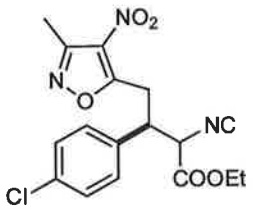
(3*S*)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-*p*-tolylbutanoate (*ent*-2.19b).



Following the general procedure using ethylisocyanoacetate and catalyst **2.39'** (6.0 mg, 0.010 mmol, 10 mol%) for 52 h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 77% yield (dr 1:1) as yellow oil.

Spectral data were identical to compound **2.19b**.

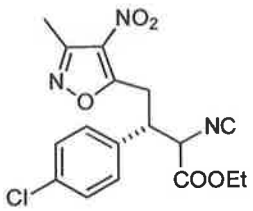
(3*R*)-ethyl 3-(4-chlorophenyl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)butanoate (2.19c).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (5.76 mg, 0.010 mmol, 10 mol%) for 58h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 80% yield (dr 1:1) as yellow oil.

IR 2982, 2136 1746, 1518; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.7.23 (m, 4H), 7.22-7.17 (m, 4H), 4.54 (d, J= 4.4, 1H), 4.42 (d, J= 4.8, 1H), 4.17 (dq, J= 6.8, J= 0.8, 2H), 4.07 (q, J= 6.8, 2H), 3.92-3.80 (m, 4H), 3.65-3.60 (m, 2H), 2.45 (s, 3H), 2.41 (s, 3H), 1.20 (t, J= 7.2, 3H), 1.10 (t , J=7.2, 3H); ^{13}C ($CDCl_3$, 400 MHz) δ 170.9, 170.7, 164.7, 164.3, 155.8, 155.7, 137.1, 135.1, 134,9, 134.3, 133.2, 132.9, 129.5, 129.4, 129.2, 129.1, 63.5, 63.2, 44.0, 43.5, 30.2, 28.4, 13.9, 11.6; HRMS found:$[M-H]^-$ 376.0840, $C_{17}H_{15}ClN_3O_5$, requires: 376.0700; m/z: 376 (100%, $[M-H]^-$).

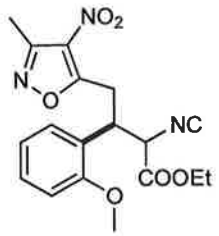
(3*S*)-ethyl 3-(4-chlorophenyl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)butanoate (*ent*-2.19c).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38'** (5.76 mg, 0.010 mmol, 10 mol%) for 58h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 70% yield (dr 1:1) as yellow oil.

Spectral data were identical to compound **2.19c**.

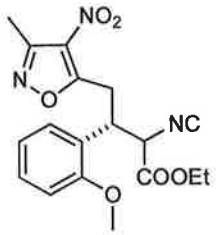
(3*R*)-ethyl 2-isocyano-3-(2-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl) butanoate (2.19d).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (5.76 mg, 0.010 mmol, 10 mol%) for 120h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 75% yield (dr 2:1) as yellow oil.

IR 2999, 2153, 1737, 1510; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02-7.163 (m, 4H), 7.10-7.07 (dd, J= 1.2, 2H), 6.83-6.76 (m, 6H), 4.75 (d, J=6.8, 3H), 4.18-4.09 (m, 5H), 4.08-4.03 (q, J= 4.4, J=11.2, 4H), 3.96 (dd, J= 10.4, J= 14.8, 2H), 3.85 (dd, J= 9.8, J= 14.9, 1H), 3.78 (s, 6H), 3.75 (s, 3H), 3.60 (dd, J= 4.8, J= 14.8, 3H), 2.41 (s, 3H), 2.39 (s, 6H), 1.16 (t, J= 7.2, 3H), 1.08 (t, J= 7.2, 6H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.9, 171.8, 165.3, 165.3, 162.0, 161.8, 157.0, 157.0, 155.5, 155.5, 129.9,129.9, 129.3, 129.2, 123.4, 123.3, 121.0, 120.9, 110.9, 62.9, 62.8, 59.7, 59.2, 55.4, 55.4, 41.0, 40.3, 28.8, 27.4, 13.9, 13.8, 11.6; HRMS found:$[M-H]^-$ 372.1206, $C_{18}H_{18}N_3O_6$, requires: 372.1196; m/z: 372 (100%, $[M-H]^-$).

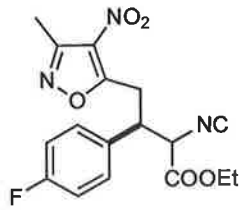
(3*S*)-ethyl 2-isocyano-3-(2-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl) butanoate (*ent*-2.19d).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (5.76 mg, 0.010 mmol, 10 mol%) for 120h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 75% yield (dr 2:1) as yellow oil.

Spectral data were identical to compound **2.19d**.

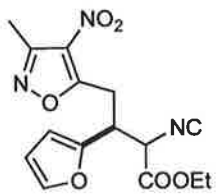
(3*R*)-ethyl 3-(4-fluorophenyl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)butanoate (2.19e).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (5.76 mg, 0.010 mmol, 10 mol%) for 26h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 80% yield (dr 1:1) as yellow oil.

IR 2972, 2155, 1746, 1518; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.20 (m, 4H), 6.98-6.93 (m, 4H), 4.55 (d, J= 4.4, 1H), 4.41 (d, J= 4.8, 1H), 4.16 (dq, J= 1.2, J= 7.2, 2H), 4.07 (dq, J= 1.2, J= 7.2, 2H), 3.93-3.80 (m, 4H), 3.65-3.61 (m,2H), 2.45 (s, 3H), 2.41 (s, 3H), 1.19 (t, J=7.2, 3H), 1.09 (t, J=7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.0, 170.9, 164.8, 164.4, 155.8, 155.7, 130.0, 129.9, 129.6, 129.5, 116.3, 116.1, 115.9, 63.4, 63.1, 44.0, 43.4, 30.4, 28.7, 13.9, 11.5; HRMS found:[M-H]$^-$ 360.0981, $C_{17}H_{15}FN_3O_5$, requires: 360.0996; m/z: 360 (100%, [M-H]$^-$).

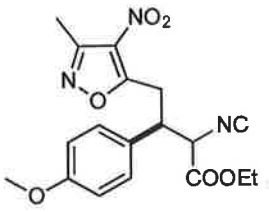
(3*S*)-ethyl 3-(furan-2-yl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)butanoate (2.19f).



Following the general procedure using ethylisocyanoacetate and catalyst **2.39** (6 mg, 0.010 mmol, 10 mol%) for 183h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 75% yield (dr 1:1) as yellow oil.

IR 2994, 2158, 1745, 1533; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.3-7.29 (m, 2H), 6.25 (t, J= 1.6, 4H), 4.6 (d, J= 4.8, 1H), 4.51 (d, J= 4.4, 1H), 4.25-4.16 (m, 4H), 4.03-4.00 (m, 2H), 3.85-3.73 (m, 2H), 3.63-3.54 (m, 2H), 2.48 (s, 3H), 2.46 (s, 3H), 1.25 (t, J= 7.2, 3H), 1.20 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 170.9, 170.7, 164.6, 164.4, 163.5, 163.3, 155.8, 155.7, 149.0, 148.3, 143.2, 143.2, 110.7, 110.6, 109.2, 108.9, 63.5, 63.3, 59.7, 59.5, 39.0, 38.9, 29.7, 28.6, 27.2, 13.9, 11.6; HRMS found:[M-H]$^-$ 332.0891, $C_{15}H_{14}N_3O_6$, requires: 332.0883; m/z: 332 (100%, :[M-H]$^-$).

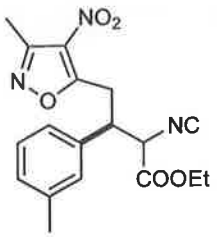
(3*R*)-ethyl 2-isocyano-3-(4-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl) butanoate (2.19g).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (7.56 mg, 0.010 mmol, 10 mol%) for 48h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 72% yield (dr 1:1) as yellow oil.

IR 2994, 2156, 1753, 1520; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15-7.13 (m, 4H), 6.78-6.75 (m, 4H), 4.51 (d, J= 4, 1H), 4.39 (d, J= 3.2, 1H), 4.39-4.12 (m, 2H), 4.09-4.04 (m, 2H), 3.86-3.83 (m, 4H), 3.71 (s, 3H), 3.70 (s, 3H), 3.61-3.56 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 1.81 (t, J= 7.2, 3H), 1.10 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.4, 171.3, 165.0, 164.6, 163.4, 163.0, 159.9, 159.8, 155.7, 155.6, 129.2, 128.9, 127.6, 126.5, 114.5, 114.3, 63.2, 63.0, 62.0, 61.1, 55.3, 55.2, 44.1, 43.5, 30.4, 29.7, 28.7, 13.9, 13.9, 11.6, 11.6; HRMS found:$[M-H]^-$ 372.1201, $C_{18}H_{18}N_3O_6$, requires: 372.1196; m/z: 372 (100%, $[M-H]^-$).

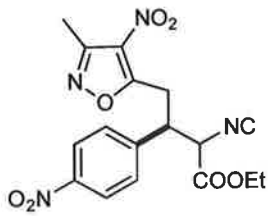
(3*R*)-ethyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-*m*-tolylbutanoate (2.19h).



Following the general procedure using ethylisocyanoacetate and catalyst **2.39** (6.00 mg, 0.010 mmol, 10% mol) for 22h at -20° C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 78% yield (dr 1:1) as yellow oil.

IR 2992, 2155, 1753, 1520; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16-7.11 (m, 2H), 7.04-7.01 (m, 6H), 4.52 (d, J= 4.4, 1H), 4.42 (d, J= 4.4, 1H), 4.15 (dq, J= 7.2, J= 0.8, 2H), 4.10-4.04 (m, 2H), 3.86-3.83 (m, 4H), 3.64-3.58 (m, 2H), 2.45 (s, 3H), 2.41 (s, 3H), 2.25 (s, 6H), 1.17 (t, J= 6.8, 3H), 1.08 (t, J= 7.2, 3H).^{13}C ($CDCl_3$, 100.6 MHz) δ 171.4, 171.2, 165.0, 164.6, 155.8, 155.6, 138.9, 138.6, 135.8, 134.7, 129.7, 129.6, 129.0, 128.8, 128.4, 125.1, 124.7, 63.3, 63.0, 44.7, 44.1, 30.2, 28.55, 21.4, 21.39, 13.9, 11.6; HRMS found:$[M-H]^-$ 356.1237, $C_{18}H_{18}N_3O_5$, requires: 356.1246; m/z: 356 (100%, $[M-H]^-$).

(3*R*)-ethyl2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-(4-nitrophenyl)butanoate (2.19i).

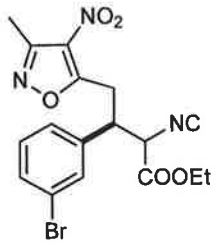


Following the general procedure using ethylisocyanoacetate and catalyst **2.39** (6.0 mg, 0.010 mmol, 10 mol%) for 46h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 88% yield (dr 1:1) as yellow oil.

IR 2981, 2158, 1739, 1530, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, J= 8.8, 1H), 8.17-8.14 (m, 3H), 7.75 (d, J= 8.8, 1H), 7.48-7.45 (m, 3H), 4.61 (d, J= 4.8, 1H), 4.46 (d, J= 4.8, 1H), 4.22 (dq, J= 7.2, J= 1.6, 2H), 4.10 (q, J= 7.2, 2H), 4.06-4.02 (m, 2H), 3.92-3.85 (m, 2H), 3.73- 3.64 (m, 2H), 2.46 (s, 3H), 2.42 (s, 3H), 1.23 (t, J= 7.2, 3H), 1.12 (t, J=

7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 170.2, 170.1, 164.8, 164.5, 164.3, 164.0, 155.9, 155.8, 148.3, 148.2, 143.0, 141.9, 139.6, 129.4, 129.0, 128.9, 124.4, 124.4, 124.1, 114.7, 63.8, 63.5, 44.2, 43.6, 30.07, 28.2, 13.9, 11.6, 11.5; HRMS found:$[M-H]^-$ 387.0923, $C_{17}H_{15}N_4O_7$, requires: 387.0941; m/z: 387 (100%, :$[M-H]^-$).

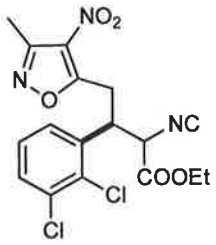
(3*R*)-ethyl 3-(3-bromophenyl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl) butanoate (2.19j).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (7.56 mg, 0.010 mmol, 10 mol%) for 30h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 64% yield (dr 1:1) as yellow oil.

IR 2951, 2153, 1729, 1534, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49 (quintet, J= 1.8, J= 1.2, J= 3, 1H), 7.47 (quintet, J= 1.8, J= 1.2, J= 3, 1H), 7.44 (t, J= 1.5, 1H), 7.41 (t, J= 1.5, 1H), 7.32 (tt, J= 1.2, J= 9, 2H), 7.29-7.23 (m, 2H), 4.63 (d, J= 4.5, 1H), 4.50 (d, J= 4.8, 1H), 4.28 (dq, J= 0.9, J= 8.1, 2H), 4.18 (q, J= 7.2, 2H), 3.99-3.86 (m, 4H), 3.78-3.66 (m, 2H), 2.55 (s, 3H), 2.51 (s, 3H), 1.29 (t, J= 7.2, 3H), 1.20 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 75.4 MHz) δ 171.0, 170.8, 167.4, 164.8, 164.5, 164.0, 156.1, 155.9, 138.4, 137.2, 132.4, 132.4, 131.7, 131.2, 131.0, 130.8, 126.7, 126.4, 123.3, 123.1, 63.8, 63.5, 61.8, 60.9, 44.5, 43.9, 30.2, 28.6, 14.1, 11.8, 11.8. HRMS found:$[M-H]^-$ 420.0204, $C_{17}H_{15}BrN_3O_5$, requires: 420.0195; m/z: 420 (100%, :$[M-H]^-$).

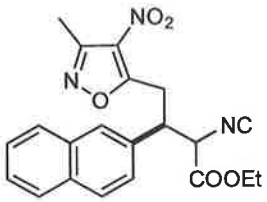
(3*R*)-ethyl3-(2,3-dichlorophenyl)-2-isocyano-4-(3-methyl-4-nitroisoxazol-5 yl) butanoate (2.19k).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (5.76 mg, 0.010 mmol, 10 mol%) for 48h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 61% yield (dr 1:0.4) as yellow oil.

IR 2964, 2145, 1740, 1522, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (dt, J= 0.8, J= 8.0, 2.4H), 7.23-7.19 (m, 1.8H), 4.55 (m, 0.4H), 4.53 (d, J= 3.6, 1H), 4.27 (q, J= 6.8, 2H), 4.15-4.03 (m, 1.2H), 3.85 (dd, J=10.4, J= 15.2, 1H), 3.74 (t, J= 9.6, 0.8H), 3.57 (dd, J= 4.8, J= 15.2, 1H), 2.46 (s, 1.2H), 2.43 (s, 3H),1.28 (t, J= 7.2, 3H), 1.10 (t, J= 7.2, 1.2H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 170.5, 170.3, 164.6, 164.1, 163.6, 155.8, 155.8, 135.7, 135.4, 134.0, 132.3, 130.9, 130.9, 127.9, 126.6, 63.7, 63.3, 60.2, 59.4, 40.6, 29.4, 26.9, 14.0, 13.7, 11.6; HRMS found:$[M-H]^-$ 410.0309, $C_{17}H_{14}Cl_2N_3O_5$, requires: 410.0311; m/z: 410 (100%, $[M-H]^-$).

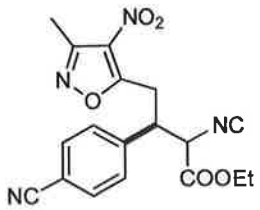
(3*R*)-2-Isocyano-4-(3-methyl-4-nitro-isoxazol-5-yl)-3-naphthalen-2-yl-butyric acid ethyl ester (2.19l).



Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (5.76 mg, 0.010 mmol, 10 mol%) for 65h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 80% yield (dr 1:1) as yellow oil.

IR 2970, 2145, 1735, 1533, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76-7.72 (m, 6H), 7.68-7.67 (m, 2H), 7.43-7.40 (m, 4H), 7.36 (dt ,J= 1.6, J= 8.8, 2H), 4.62 (d, J= 4.8, 1H), 4.52 (d, J= 4.8, 1H), 4.16-3.97 (m, 8H), 3.74-3.65 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.12 (t, J= 7.2, 3H), 1.01 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.2, 171.1, 164.9, 164.6, 163.8, 163.4, 155.8, 155.6, 133.3, 133.2, 133.2, 133.1, 130.7, 129.2, 128.9, 128.1, 127.9, 127.7, 127.3,126.7, 126.7, 126.6, 125.2, 124.9, 63.4, 63.1, 44.9, 44.3, 30.9, 30.3, 29.7, 28.5, 14.0, 13.9, 11.6, 11.5; HRMS found:$[M-H]^-$ 392.1238, $C_{21}H_{18}N_3O_5$, requires: 392.1249; m/z: 392 (100%, $[M-H]^-$).

(3*R*)-3-(4-Cyano-phenyl)-2-isocyano-4-(3-methyl-4-nitro-isoxazol-5-yl)-butyric acid ethyl ester (2.19m).

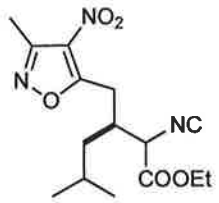


Following the general procedure using ethylisocyanoacetate and catalyst **2.38** (5.76 mg, 0.010 mmol, 10 mol%) for 48 h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 76% yield (dr 1:1) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60-7.57 (m, 4H), 7.41-7.38 (m, 4H), 4.59 (d, J= 4.4, 1H), 4.44 (d, J= 4.8, 1H), 4.20 (q, J= 2, J= 7.2, 2H), 4.08 (q, J= 7.2, J= 14.4, 2H), 4.00-

3.96 (m, 2H), 3.85 (m, 2H), 3.66 (m, 2H), 2.46 (s, 3H), 2.42 (s, 3H), 1.22 (t, J= 7.2, 3H), 1.10 (t, J= 7.2, 3H). ^{13}C ($CDCl_3$, 100.6 MHz) δ 170.4, 170.2, 164.6, 164.4, 164.3, 155.9, 155.8, 141.2, 140.0, 133.0, 132.7, 129.1, 128.7, 118.0, 117.9, 113.2, 113.1, 63.7, 63.4, 61.1, 60.3, 44.4, 43.9, 30.0, 29.7, 28.1, 14.1, 13.9, 11.6, 11.5; HRMS found:$[M-H]^-$ 367.1038, $C_{18}H_{15}N_4O_5$, requires: 367.1042; m/z: 367 (100%, $[M-H]^-$).

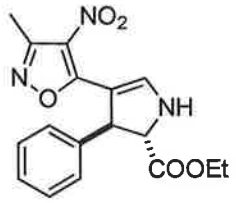
(3*S*)-ethyl 2-isocyano-5-methyl-3-((3-methyl-4-nitroisoxazol-5-yl)methyl)hexanoate (2.19n).



Following the general procedure using ethylisocyanoacetate and catalyst **2.39n** (5.76 mg, 0.010 mmol, 10 mol%) for 48h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 88% yield (dr 1:1) as yellow oil.

^1H NMR ($CDCl_3$, 400 MHz) δ 4.35 (d, J= 2.8, 1H), 4.25-4.18 (m, 5H), 3.41 (dd, J= 0.8, 1H), 3.26-3.13 (m, 3H), 2.69-2.67 (m, 2H), 2.69 (s, 3H), 2.67 (m, 3H), 1.58-1.50 (m, 3H), 1.42-1.25 (m, 6H), 1.25-1.15 (m, 3H), 0.89-0.87 (m, 6H), 0.84-0.81 (m, 6H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 172.2, 172.1, 165.7, 165.3, 162.4, 162.3, 156.0, 155.9, 63.3, 63.1, 60.0, 58.9, 40.3, 38.9, 37.2, 36.7, 29.1, 28.3, 25.0, 25.0, 23.3, 23.0, 21.6, 21.6, 14.1, 14.0, 11.7; HRMS found:$[M-H]^-$ 322.1478, $C_{18}H_{15}N_4O_5$, requires: 322.1481; m/z: 322 (100%, $[M-H]^-$).

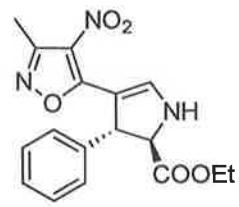
(2*S*,3*S*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20a)



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 67% yield as yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 18.2 min, t_{min} = 26.7 min, 97% *ee*).

mp 54°C; $[\alpha]_D^{20}$ = + 54 (c = 0.84 in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.76 (dd, J= 0.6, J=3.6, 1H), 7.33-7.31 (m, 2H), 7.30-7.22 (m, 3H), 5.69 (s, 1H), 4.81 (d, J=3.9, 1H), 4.40 (d, J=3.9, 1H), 4.39-4.25 (m, 2H), 2.46 (s, 3H), 1.36 (t, J=7.2, 3H); ^{13}C ($CDCl_3$, 75.4 0MHz) δ 171.5, 166.2, 156.5, 151.4, 142.6, 129.2, 127.8, 127.1, 102.7, 68.8, 62.6, 50.8, 14.4, 12.6; HRMS found:$[M-H]^-$ 342.0920, $C_{17}H_{16}N_3O_5$, requires: 342.1090; m/z: 342 (100%, $[M-H]^-$).

(2*R*,3*R*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (*ent*-2.20a).

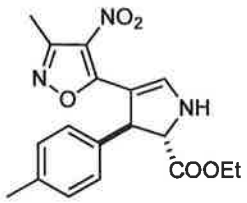


Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 72% yield as yellow

solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 31.8 min, t_{min} = 19.8 min, 74% *ee*).

$[\alpha]_D^{20}$ = - 59 (c = 0.84 in $CHCl_3$); Spectral data were identical to compound **2.20a**.

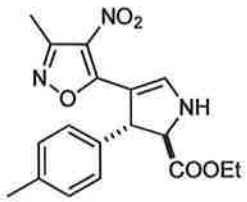
(2*S*,3*S*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-*p*-tolyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20b).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 76% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 19.5 min, t_{min} = 26.9 min, 92% *ee*).

$[\alpha]_D^{20}$ = + 86 (c = 0.54 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.6 (d, J= 3.2, 1H), 7.13 (d, J= 8, 2H), 7.04 (d, J= 8, 2H), 5.52 (s, 1H), 4.69 (d, J= 3.6, 1H), 4.31 (d, J= 4, 1H), 4.27-4.18 (m sistema ABX, 2H), 2.38 (s, 3H), 2.23 (s, 3H), 1.28 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.4, 150.9, 139.5, 137.2, 129.6, 126.8, 102.8, 68.7, 62.3, 50.2, 21.0, 14.2, 12.3; HRMS found:$[M-H]^-$ 356.1237, $C_{18}H_{18}N_3O_5$, requires: 356.1246; m/z: 356 (100%, $[M-H]^-$).

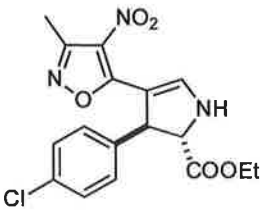
(2*R*,3*R*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-*p*-tolyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (*ent*-2.20b).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 75% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 25.6 min, t_{min} = 18.9 min, 62% *ee*).

$[\alpha]_D^{20}$ = - 80 (c = 0.50 in $CHCl_3$); spectral data were identical to compound **2.20b**.

(2*S*,3*S*)-ethyl 3-(4-chlorophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20c).

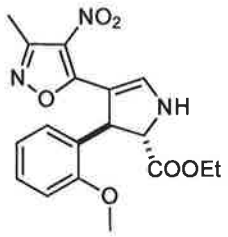


Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 62% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 19.8 min, t_{min} = 27.4 min, 96% *ee*).

$[\alpha]_D^{20}$ = + 71 (c= 0.72 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (d, J= 2.7, 1H), 7.31-7.24 (m, 4H), 5.66 (s, 1H), 4.79 (d, J= 4.2, 1H), 4.39-4.23 (m, 3H), 4,6 (s, 3H), 1.36

(t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 75.4 MHz) δ 171.2, 166.0, 156.6, 151.2, 141.1, 133.6, 129.4, 128.5, 102.4, 68.6, 62.7, 50.2, 14.4, 12.6; HRMS found:$[M-H]^-$ 376.0749, $C_{17}H_{15}ClN_3O_5$, requires: 376.0700; m/z: 376 (100%, $[M-H]^-$).

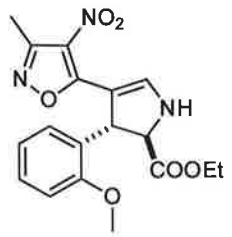
(2*S*,3*S*)-ethyl 3-(2-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20d).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 67% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 25.3 min, t_{min} = 33.7 min, 96% *ee*).

$[\alpha]_D^{20}$ = + 54 (c= 0.52 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (dd, J= 0.6, J=3.6, 1H), 7.26-7.20 (m, 1H), 7.07 (dd, J=1.8, J=7.8, 1H), 6.94-6.84 (m, 2H), 5.62 (s, 1H), 5.19 (d, J=3.6, 1H), 4.37-4.19 (m, 3H), 3.89 (s, 3H), 2.47 (s, 3H), 1.36 (t, J=7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.4, 166.2, 156.9, 156.2, 151.8, 129.6, 128.6, 127.5, 124.7, 120.8, 111.0, 101.1, 67.8, 62.0, 55.3, 44.5, 14.2, 12.4. HRMS found:$[M-H]^-$ 372.1206, $C_{18}H_{18}BrN_3O_6$, requires: 372.1196; m/z: 372 (100%, :$[M-H]^-$).

(2*R*,3*R*)-ethyl 3-(2-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*- pyrrole-2-carboxylate (*ent*-2.20d).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 67% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 30.7 min, t_{min} = 23.5 min, 92% *ee*).

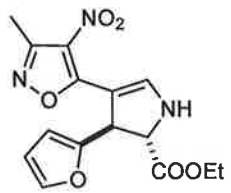
$[\alpha]_D^{20}$ = - 45 (c= 0.59 in $CHCl_3$); spectral data were identical to compound **2.20d**.

(2*S*,3*S*)-ethyl 3-(4-fluorophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20e).

Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 73% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 18.6 min, t_{min} = 29.6 min, 88% *ee*).

$[\alpha]_D^{20}$ = + 79 (c = 0.77 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65 (s, 1H), 7.23-7.20 (m, 2H), 6.95-6.91 (m, 2H), 5.54 (s, 1H), 4.72 (d, J= 3.6, 1H), 4.28 (d, J= 3.6, 1H), 4.27-4.19 (m, 2H), 2.39 (s, 3H), 1.29 (t, J= 6.8, 3H); ^{13}C ($CDCl_3$, 100.6MHz) δ 171.2, 156.4, 150.9, 138.3, 128.6, 128.5, 116.0, 115.8, 102.5, 68.6, 62.4, 49.9, 29.7, 14.2, 12.3; HRMS found:$[M-H]^-$ 360.1003, $C17H15FN_3O_5$, requires: 360.0996; m/z: 360 (100%, $[M-H]^-$).

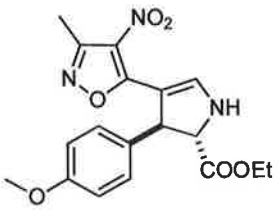
(2*S*,3*S*)-ethyl 3-(furan-2-yl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20f).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 63% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 21.3 min, t_{min} = 23.5 min, 90% *ee*).

$[\alpha]_D^{20}$ = + 65 (c = 1.22 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.59 (s, 1H), 7.26 (dd, J= 1.6, J= 0.8, 1H), 6.22 (dd, J= 3.2, J= 1.6, 1H), 6.10 (d, J= 3.2, 1H), 5.57 (s, 1H), 4.90 (d, J= 3.6, 1H), 4.52 (d, J= 4.0, 1H), 4.27-4.19 (m, 2H), 2.43 (s, 3H), 1.28 (t, 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 170.9, 165.9, 156.4, 153.5, 151.1, 142.1, 110.6, 106.7, 99.4, 65.4, 62.5, 44.0, 29.7, 14.2, 12.4, HRMS found:$[M-H]^-$ 372.1203, $C_{18}H_{18}N_3O_6$, requires: 372.1196; m/z: 372 (100%, $[M-H]^-$).

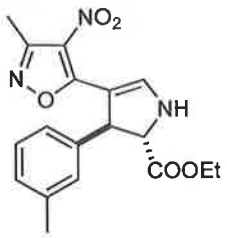
(2*S*,3*S*)-ethyl3-(4-methoxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20g).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 67% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 23.4 min, t_{min} = 33.4 min, 89% *ee*).

$[\alpha]_D^{20}$ = + 93 (c = 0.47 in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.71 (d, J=3.3, 1H), 7.25-7.23 (m, J=3.0, J=2.1, 1H), 7.21 (m, J=2.1, J=3.0, 1H), 6.85-6.84 (m, J=3.0, J=2.1, 1H), 6.82-6.81 (m, J=3.0, J=2.1, 1H), 5.60 (d, J=2.7, 1H), 4.36 (d, J=3.9, 1H), 4.33-4.23 (m sistema ABX, 2H), 3.77 (s, 3H), 2.45 (s, 3H), 1.34 (t, J=7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.4, 166.1, 158.9, 156.3, 150.8, 134.6, 114.3, 102.9, 68.7, 62.3, 55.3, 49.9, 14.2, 12.4. HRMS found:$[M-H]^-$ 372.1206, $C_{18}H_{18}N_3O_6$, requires: 372.1196; m/z: 372 (100%, :$[M-H]^-$).

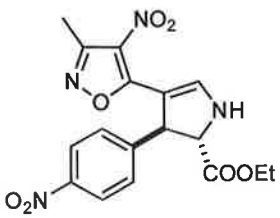
(2*S*,3*S*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-*m*-tolyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20h)



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 54% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 17.6 min, t_{min} = 30.9 min, 93% *ee*).

$[\alpha]_D^{20}$ = + 78 (c = 0.71 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67 (s, 1H), 7.14-7.10 (m, 1H), 7.04-7.03 (m, 2H), 6.98 (d, J= 7.6, 1H), 5.32 (s, 1H), 4.68 (d, J= 3.6, 1H), 4.31 (d, J= 4.0, 1H), 4.27-4.18 (m, 2H), 2.39 (s, 3H), 2.25 (s, 3H), 1.28 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 151.0, 128.9, 128.3, 127.5, 123.9, 68.7, 65.9, 62.3, 50.5, 29.7, 22.4, 21.5, 15.3, 14.2, 14.1, 12.4. HRMS found:$[M-H]^-$ 356.1253, $C_{18}H_{18}N_3O_5$, requires: 356.1246; m/z: 356 (100%, $[M-H]^-$).

(2*S*,3*S*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-(4-nitrophenyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20i).

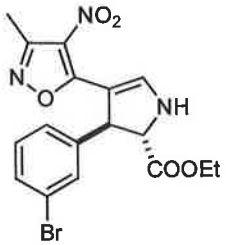


Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 58% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 39.3 min, t_{min} = 45.9 min, 88% *ee*).

$[\alpha]_D^{20}$ = + 87 (c = 0.75 in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 8.20 (t, J=2.4, J=1.8, 2H), 8.17 (t, J=2.1, J=2.4, 2H), 5.68 (s, 1H), 4.92 (d, J=4.2, 1H), 4.37 (d, J=4.2, 1H), 4.38-4.27 (m, 2H), 2.46 (s, 3H), 1.368 (t, J=6.9, 3H); ^{13}C ($CDCl_3$, 75.4 MHz) δ 170.7, 165.7, 156.7, 151.3, 149.7, 147.6, 128.2, 124.6, 101.7, 68.2, 63.0, 50.5, 14.4,

12.5. HRMS found:[M-H]$^-$ 387.0938, $C_{17}H_{15}N_4O_7$, requires: 387.0941; m/z: 387 (100%, [M-H]$^-$).

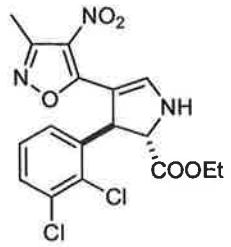
(2*S*,3*S*)-ethyl 3-(3-bromophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20j).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 61% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 20.6 min, t_{min} = 38.2 min, 56% *ee*).

$[\alpha]_D^{20}$ = + 64 (c = 0.43 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (d, J=3, 1H), 7.43 (t, J=1.8, 1H), 7.39-7.35 (m, 1H), 7.27-7.23 (m, 1H), 7.17 (t, J=7.8, 1H), 5.72 (s, 1H), 4.75 (d, J=3.9, 1H), 4.35 (d, J=4.2, 1H), 4.37-4.22 (m, 2H), 2.45 (s, 3H), 1.35 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 75.4 MHz) δ 171.1, 166.0, 156.6, 151.5, 144.8, 131.0, 130.8, 130.1, 126.0, 123.3, 102.1, 68.6, 62.7, 50.4, 14.4, 12.1. HRMS found:[M-H]$^-$ 420.0204, $C_{17}H_{15}BrN_3O_5$, requires: 420.0195; m/z: 420 (100%, :[M-H]$^-$).

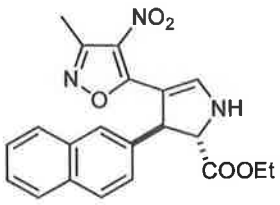
(2*S*,3*R*)-3-(2,3-Dichloro-phenyl)-4-(3-methyl-4-nitro-isoxazol-5-yl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid ethyl ester (2.20k).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 58% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 18.7 min, t_{min} = 20.7 min, 88% *ee*).

$[\alpha]_D^{20}$ = + 34 (c = 0.25 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.72 (d, J= 2.4, 1H), 7.31 (dd, J= 8, J= 1.6, 1H), 7.06 (t, J= 7.6, 1H), 6.99-6.96 (m, 1H), 5.55 (s, 1H), 4.24 (m, 4H), 2.40 (s, 3H), 1.29 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 170.6, 165.6, 151.7, 129.7, 127.7, 62.5, 53.4, 29.7, 14.1, 12.3; HRMS found:$[M-H]^-$ 410.0308, $C_{17}H_{14}Cl_2N_3O_5$, requires: 410.0311; m/z: 410 (100%, $[M-H]^-$).

(2*S*,3*S*)-4-(3-Methyl-4-nitro-isoxazol-5-yl)-3-naphthalen-2-yl-2,3-dihydro-1H-pyrrole-2-carboxylic acid ethyl ester (2.20l).

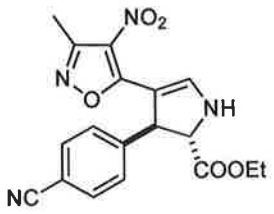


Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 64% yield as yellow

oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 22.8 min, t_{min} = 33.8 min, 86% *ee*).

$[\alpha]_D^{20}$ = + 47 (c = 0.95 in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 7.75-7.68 (m, 4H), 7.41-7.36 (m, 3H), 5.62 (s, 1H), 4.90 (d, J=4, 1H), 4.39 (d, J=4, 1H), 4.32-4.19 (m, J=7.2, 2H), 2.36 (s, 3H), 1.30 (t, J=7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.5, 166.2, 156.5, 151.4, 139.6, 133.5, 132.8, 129.0, 127.9, 127.6, 126.3, 126.0, 125.7, 124.9, 102.7, 68.8, 62.6, 50.8, 29.7, 14.4, 12.6; HRMS found:$[M-H]^-$ 392.1239, $C_{21}H_{18}N_3O_5$, requires: 392.1249; m/z: 392 (100%, $[M-H]^-$).

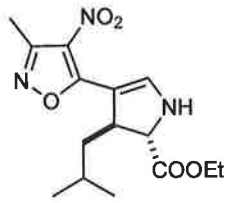
(2*S*,3*S*)-ethyl 3-(4-cyanophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20m).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 65% yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 36.4 min, t_{min} = 46.1 min, 86% *ee*).

$[\alpha]_D^{20}$ = + 75 (c = 0.38 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67 (s, 1H), 7.56 (d, J= 8.0, 2H), 7.37 (d, J=8.4, 2H), 5.69 (s, 1H), 4.79 (d, J= 4, 1H), 4.28 (d, J= 4.4, 1H), 4.24 (m, 2H), 2.39 (s, 3H), 1.29 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 170.6, 165.6, 156.5, 151.3, 147.6, 132.94, 127.9, 111.6, 101.4, 68.1, 62.7, 50.5, 29.7, 14.2, 12.3; HRMS found:$[M-H]^-$ 367.1040, $C_{18}H_{15}N_4O_5$, requires: 367.1042; m/z: 367 (100%, $[M-H]^-$).

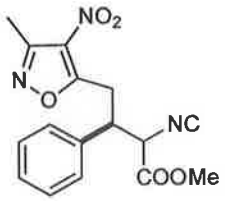
(2*S*,3*S*)-ethyl 3-isobutyl-4-(3-methyl-4-nitroisoxazol-5-yl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.20n).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 61 % yield as yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 13.1 min, t_{min} = 13.8 min, 77% *ee*).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (s, 1H), 4.20-4.16 (m, 3H), 3.71-3.63 (m, 2H), 2.50-2.48(m, 1H), 2.47 (s, 3H), 1.82-1.78 (m, 2H), 1.26 (t, J= 7.3, 3H), 1.02 (d, J= 6.8, 3H), 0.91 (d, J= 6.4, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 172.1, 166.1, 156.5, 151.0, 103.2, 64.7, 62.1, 43.9, 43.0, 25.4, 23.8, 20.9, 14.1, 12.5 ; HRMS found:$[M-H]^-$ 322.1480, $C_{18}H_{15}N_4O_5$, requires: 322.1481; m/z: 322 (100%, $[M-H]^-$).

(3*R*)-methyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl butanoate (2.41a).

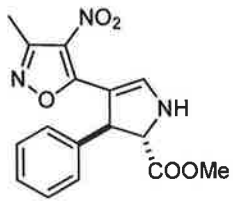


Following the general procedure using methylisocyanoacetate and catalyst **2.39** (6 mg, 0.010 mmol, 10 mol%) for 48 h at -20°C. The product was purified on silica gel (ethyl

ether/petroleum ether 50:75) and the title compound was obtained in 73% yield (dr 1:1) as yellow oil.

IR 2984, 2156, 1754, 1527; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.20 (m, 10H), 4.57 (d, J= 4.4, 1H), 4.46 (d, J= 4.4, 1H), 3.93-3.82 (m, 4H), 3.72 (s, 3H), 3.67-3.62 (m, 2H), 3.61 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.2, 171.1, 165.5, 165.1,163.7, 163.5, 155.8, 155.6, 135.9, 134.7, 128.0, 128.6, 61.7, 60.9, 53.8, 53.5, 44.7, 44.2, 31.9, 28.4, 11.6, 11.6, HRMS found:$[M-H]^-$ 328.0920, $C_{16}H_{14}N_3O_5$, requires: 328.0933; m/z: 370 (100%, $[M-H]^-$).

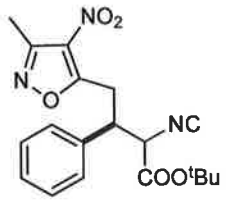
(2*S*,3*S*)-4-(3-Methyl-4-nitro-isoxazol-5-yl)-3-phenyl-2,3-dihydro-1H-pyrrole-2-carboxylic acid methyl ester (2.42a).



Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 67 % yield as yellow oil. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 33.6 min, t_{min} = 22.0 min, 68% *ee*).

$[\alpha]_D^{20}$ = + 89 (c = 0.52 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.67 (s, 1H), 7.25-7.24 (m, 5H), 5.23 (s, 1H), 4.74 (d, J= 3.6, 1H), 4.35 (d, J= 3.6, 1H), 3.79 (s, 3H), 2.38 (s, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.8, 166.0, 156.3, 150.9, 142.3, 129.0, 127.6, 126.9, 102.7, 68.5, 53.2, 50.5, 29.7, 12.4, HRMS found:$[M-H]^-$ 328.0932, $C_{16}H_{14}N_3O_5$, requires: 328.0933; m/z: 370 (100%, $[M-H]^-$).

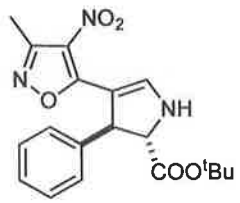
(3*R*)-*tert*-butyl 2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylbutanoate (2.41b).



Following the general procedure using methylisocyanoacetate and catalyst **2.39** (6 mg, 0.010 mmol, 10 mol%) for 117h at -20°C. The product was purified on silica gel (ethyl ether/petroleum ether 50:75) and the title compound was obtained in 42% yield as 2 diastereoisomer (dr 1:1) as yellow oil.

IR 2965, 2151, 1749, 1536; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.17 (m, 10H), 4.46 (d, J= 4.4, 1H), (d, J= 4.4, 1H), 3.91-3.81 (m, 4H), 3.65-3.55 (m, 2H), 2.44 (s, 3H), 2.44 (s, 3H), 1.32 (s, 9H), 1.24 (s, 9H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 171.3, 171.3, 163.7, 163.3, 155.7, 155.6, 135.8, 135.1, 129.1, 128.9, 128.8, 128.3, 127.9, 84.8, 84.7, 45.0, 44.0, 30.6, 29.1, 27.9, 27.6, 11.6, 11.6; HRMS found:$[M-H]^-$ 370.1548, $C_{19}H_{20}N_3O_5$, requires: 370.1403; m/z: 370 (100%, $[M-H]^-$).

(2*S*,3*S*)-*tert*-butyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (2.42b).

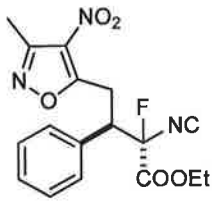


Following the general procedure the product was purified on silica gel (ethyl ether/petroleum ether 1:1) and the title compound was obtained in 61 % yield as yellow

solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.5 mL/min, t_{maj} = 13.0 min, t_{min} = 17.2 min, 78% *ee*).

$[\alpha]_D^{20}$ = + 24 (c = 0.24 in $CHCl_3$);^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (d, J= 4.4, 1H), 7.31-7.27 (m, 4H), 7.25-7.23 (m, 1H), 5.62 (s, 1H), 4.74 (d, J= 5.6, 1H), 4.29 (d, J= 5.2, 1H), 2.45 (s, 3H), 1.53 (s, 9H); ^{13}C ($CDCl_3$, 75.4 MHz) δ 170.6, 166.3, 156.5, 151.5, 142.9, 129.2, 127.6, 127.1, 108.0, 102.5, 83.6, 69.4, 50.9, 28.3, 12.6; HRMS found:[M-H]$^-$ 370.1187, $C_{19}H_{20}N_3O_5$, requires: 370.1403; m/z: 370 (100%, [M-H]$^-$).

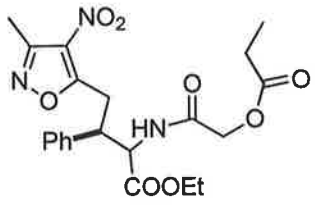
(2*S*,3*R*)-ethyl 2-fluoro-2-isocyano-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl butanoate (2.43).



To a solution of **2.19a** (20.0 mg, 0.058 mmol) in dry THF at -37°C, K_2CO_3 (9.6 mg, 0.07 mmol) was added. The solution was stirred for 30 min after NFSI (91 mg, 0.29 mmol) dissoled in dry THF was added in one portion. The mixture was stirred for 1h at the same temperature and the at rt for 24h. NH_4Cl was added and the product was extracted with Et2O (3 x 2mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent petroleum ether:EtOAc 7:1) to give **2.43** as yellow oil in 67% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.22 (m, 5H), 4.19-4.13 (m, 2H), 4.051- 3.90 (m, J= 5.6, J= 4.0, 2H), 3.68 (dd, J= 14.8, J= 4.8, 1H), 2.40 (s, 3H), 1.13 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 170.59, 137.2, 129.83; 129.8, 129.6, 129.1, 128.9, 64.4, 53.4, 49.0, 48.9, 30.9, 27.4, 13.7, 11.6; ^{19}F NMR (DMSO, 156 MHz) δ -128.2

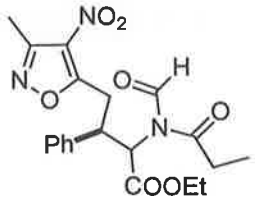
(3*R*)-Ethyl-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl-2-(2- (propanoyloxy) ethanamido) butanoate (2.44).



To a solution of **2.29a** (56 mg, 0.26 mmol) in CH_2Cl_2 (400 µL) paraformaldehyde (7.2 mg, 0.24 mmol) and propionic acid (13 µL, 0.176 mmol) were added. The solution was heated under microwave at 100°C for 6 h. The mixture was dried under reduced pressure and purified by silica gel (eluent petroleum ether:EtOAc 8:5) to give a mixture of two diastereoisomers (dr 1:1) as yellow oil. Et_2O (2 mL) was added to get **2.44** as single diastereoisomer in 41% as white solid.

^{1}H NMR ($CDCl_3$, 300 MHz) 7.31-7.28 (m, 3H), 7.17-7.14 (m, 2H), 6.49 (d, J= 9.0, 1H), 5.07 (dd, J= 9.0, J= 3.9, 1H), 4.69 (q, J= 15.6, 2H), 4.19-4.17 (m, 3H), 3.80-3.64 (m, 2H), 2.49 (s, 3H), 2.45 (q, J= 7.5, 2H), 1.29 (t, J= 6.9, 3H), 1.19 (t, J= 7.5, 3H); ^{13}C ($CDCl_3$, 75.4 MHz) δ 173.1, 172.4, 169.9, 167.9, 155.8, 136.1, 129.1, 128.7, 128.1, 62.9, 62.4, 55.1, 45.1, 30.1, 27.5, 14.4, 11.9, 9.2.

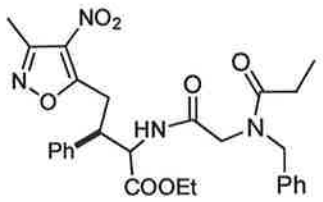
(3*R*)-Ethyl 2-(*N*-formylpropanamido)-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl butanoate (2.45).



To a solution of **2.29a** (132 mg, 0.38mmol) in dichloethane (2 mL), acetone (43 μL, 0.58 mmol) and propionic acid (43 μL, 0.58 mmol) were added. The solution was heated under microwave at 100°C for 10 h. The mixture was dried under reduced pressure and purified by silica gel (eluent petroleum ether:EtOAc 8:2) to give **2.45** a mixture of two diastereoisomers (dr 1:1) as yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.69 (s, 1H), 7.15-7.13 (m, 3H), 7.02-6.99 (m, 2H), 5.43 (d, J= 9.9, 1H), 4.38-4.31 (m, 2H), 4.23 (dd, J= 6.0, 2H), 4.07 (d, J= 4.5, 1H), 3.90 (d, J= 11.1, 1H), 3.85 (d, J= 11.4, 1H), 2.41 (s, 3H), 1.25 (t, J= 6.9, 3H), 0.92 (t, J= 7.2, 3H); ^{13}C ($CDCl_3$, 75.4 MHz) δ 173.9, 172.7, 168.8, 161.4, 155.5, 137.9, 128.6, 128.5, 128.1, 62.3, 55.4, 42.8, 33.2, 28.1, 14.3, 11.8, 8.6.

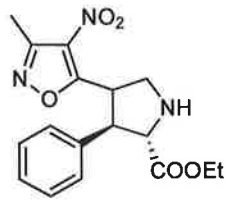
(3*R*)-Ethyl 2-(3-benzyl-3-propanoylureido)-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenyl butanoate (2.46).



To a solution of **2.29a** (66 mg, 0.19 mmol) in MeOH (432 μL), paraformaldehyde (8.7 mg, 0.29mmol), propionic acid (16 μL,0.21 mmol) and benylamine (31.5 μL,0.29 mmol) were added. The solution was stirred for 96 h. The mixture was dried under reduced pressure and the product purified by silica gel (eluent petroleum ether:EtOAc 6:4) to give **2.46** as yellow oil in 36% yield (dr 10:8).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.16 (m, 8H), 6.96 (d, J= 8.9, 1H), 6.72 (d, J= 9, 1H), 5.00 (q, J= 3, 1H), 4.87 (q, J= 6, 1H), 4.63 (s, 2H), 4.57 (s, 2H), 4.16-4.10 (m, 2H), 4.05-3.93 (m, 2H), 3.83-3.60 (m, 2H), 2.47 (s, 3H), 1.25 (t, J= 6, 3H), 1.03 (t, J= 3, 3H).

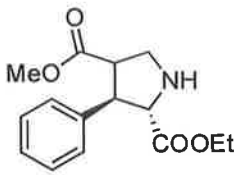
(2*S*,3*R*)-ethyl 4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylpyrrolidine-2-carboxylate (2.47).



To a solution of **2.20a** (34 mg, 0.1 mmol) in TFA (950 µL), Et_3SiH (199 µL,1.25 mmol) was added. The solution was stirred for 45 min and a solution of $NaHCO_3$ sat. (3 mL) was added at -78°C. The solution was extracted with EtOAc (3 X 3 mL) and under reduced pressure. Water was added to the yellow oil and extracted with CH_2Cl_2 (5 X 2 mL),. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent petroleum ether:EtOAc 10:8) to give **2.47** as yellow solid in 73% yield.

Rf 0.36 in petroleum ether:EtOAc 1:1; IR 2975, 1763, 1522; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.17 (m, 5H), 4.47 (q, J= 8.4, 1H), 4.19-4.11 (m, 1H), 4.10-4.02 (m, 1H), 3.96 (d, J= 8, 1H), 3.81 (t, J= 8.8, 1H), 3.67 (t, J= 10, 1H), 3.35 (t, J= 8.8, 1H), 2.81 (s, 1H), 2.43 (s, 3H), 1.105 (t, J= 7.2, 3H);^{13}C ($CDCl_3$, 100.6 MHz) δ 173.0, 172.8, 156.0, 138.8, 128.9, 127.7, 127.5, 68.0, 61.5, 54.2, 51.7, 47.1, 29.7, 14.1, 11.6; HRMS found:$[M-H]^-$ 344.1251, $C_{17}H_{19}N_3O_5$, requires: 344.1246; m/z: 344 (100%, $[M-H]^-$).

(2*S*,3*R*)-2-ethyl 4-methyl 3-phenylpyrrolidine-2,4-dicarboxylate (2.48).



To a solution of **2.47** (128 mg, 0.37 mmol) in THF (3.7 mL) a solution of $KMnO_4$ (352 mg, 2.23 mmol) dissolved in H_2O/Dioxane (13 mL/3.7 mL) was added. The solution was stirred for 45 min. After that the solution was filtered and extracted with EtOAc (3 X 3 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The acid was dissolved in MeOH (3.6 mL) and TMSDM 2.0M (0.74 mL, 1.48 mmol) was added. The solution was stirred 15 min and then concentrated under reduced pressure. The product was purified by silica gel (eluent DCM to EtOAc). The recovered product was purified a second time by silica gel using Petroleum ether : EtOAc 5:2 as eluent to give compound **2.48** in 11% yield (dr 2:1) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.31 (m, 10H), 7.24-7.18 (m, 5H), 5.30-5.26 (m, 1H), 5.09 (q, J= 8, 2H), 4.59-4.52 (m, 4H), 4.38 (dd, J= 14.4, J=8.8, 2H), 4.29-4.11 (m, 6H), 3.91-3.87 (m, 1H), 3.87-3.80 (m, 2H), 3.68 (s, 3H), 3.67 (s, 6H), 3.441-3.369 (m, J=7.6, J= 4.8, 2H), 3.27-3.20 (m, J= 8.4, J= 8.4, 1H), 1.24 (t, J= 6.8, 3H), 1.17 (t, J= 7.2, 6H); ($CDCl_3$, 100.6 MHz) δ 171.1, 170.1, 169.0, 167.4, 136.5, 129.3, 129.2, 128.4, 128.3, 127.3, 127.0, 68.1, 64.8, 62.4, 61.9, 52.8, 52.7, 52.3, 50.3, 50.2, 48.7, 47.9, 47.2, 29.7, 14.0.

2.2 References.

[1] M. Matsushita, K. Yoshida, N. Yamamoto, P. Wirsching, R. A. Lerner, K. D. Janda *Angew. Chem. Int. Ed.* **2003**, *42*, 5984

[2] S.-s. Jew, Mi-S. Yoo, B.-S. Jeong,. Il Y. Park, H.-g. Park *Org. Lett.* **2002**, *4*, 4245.

[3] A. Baschieri, L. Bernardi, A. Ricci, S. Surisetti, M. F. A. Adamo *Angew. Chem. Int. Ed.* **2009**, *48*, 9342 –9345.

[4] H. Kawai, A. Kusuda, S. Nakkamura, M. Shiro, N. Shibata *Angew. Chem. Int. Ed.* **2009**, *48*, 6324-6327

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Materials and Methods for Chapter 3.

General Methods.

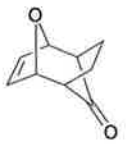
^{1}H and ^{13}C NMR Spectra were recorded on a 400 MHz spectrometer at ambient temperatures. ^{1}H NMR spectral assignments are supported by ^{1}H-^{1}H COSY and ^{13}C-^{1}H COSY where necessary. For ^{1}H NMR recorded in $CDCl_3$ chemical shifts (δH) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet, d, doublet, t, triplet, dd, doublet of doublets, dt, doublet of triplets, tt, triplet of triplets, m, multiplet and br, broad. Coupling constants (J) were recorded in Hertz (Hz) to the nearest 0.5 Hz. Carbon spectra are supported by DEPT analysis where necessary. Infrared (IR) spectra were recorded as thin films between NaCl plates. Absorption maximum (υ_{max}) was reported in wavenumbers (cm^{-1}) and only selected peaks are reported. The following abbreviations are used: w, weak, m, medium, s, strong and br, broad. High resolution mass spectra were obtained on a Waters Micro mass LCT and low resolution mass spectra were recorded on Waters Micro mass Quattro LCMS spectrometers at 70 eV. Elemental analysis was carried out using a CE440 Elemental Analyser purchased from Exeter Analytical (UK) Ltd. Optical rotations were measured on a Perkin- Elmer 241 polarimeter.

Materials

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Flash chromatography was carried out using silica gel 60 (0.040-0.063mm, 230-400 mesh) as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with silica gel 60, which were visualized by quenching of u.v. fluorescence (λ_{max} = 254 nm) or by staining with either 10% w/v ammonium molybdate in 2 M sulfuric acid or basic potassium permanganate solution (followed by heat) as appropriate.

3.1 Experimental Details for Chapter 3.

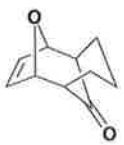
9-Oxa-Tricyclo[4.2.1.1^{2,5}]dec-7-en-10-one (3.35a).



To a solution of α-chloropentanone (1.0 mmol) and furan (5.0 mmol) in trifluoroethanol (20 mL) with vigorous stirring was added dropwise NEt_3 (2.0 mmol) at r.t. After the starting material was consumed (48 h), the solvent was removed under vacuum. Water was added to the brown solid and the product was extracted in CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give compound **3.35a** in 90 % yield as a brown solid.

Rf 0.34 in 1:3 EtOAc: Hexane IR (CCl_4) 1744 cm^{-1}; mp: 52°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 6.24 (s, 2H, C<u>H</u>=C<u>H</u>), 4.65 (m, 2H, C<u>H</u>-O-C<u>H</u>), 2.32-2.31 (m, 2H, C<u>H</u>-CO-C<u>H</u>), 1.90-1.87 (m, 2H, CH-C<u>H</u>$_2$), 1.74-1.70 (m, 2H, CH-C<u>H</u>$_2$); ^{13}C-NMR(106.6 MHz): δ_C= 210.2 (<u>C</u>=O), 132.8 (H<u>C</u>=<u>C</u>H), 82.8 (<u>C</u>H-CO-<u>C</u>H), 51.1(CH-<u>C</u>H$_2$), 21.3 (CH-<u>C</u>H$_2$).

11-Oxa-tricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (3.35b).



To a solution of α-chloropentanone (1 mmol) and furan (5 mmol) in trifluoroethanol (20 mL) with vigorous stirring was added dropwise NEt_3 (2 mmol) at rt. After the starting material was consumed (120h), the solvent was removed under vacuum. Water was added to the brown solid and the product was extracted in CH_2Cl_2. The organic layer was

dried over Na_2SO_4 and concentrated under reduced pressure to give compound **3.35b** as a yellow solid in 97% yield.

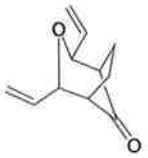
Rf 0.45 in 4:3 EtOAc: Petroleum Ether IR (CCl_4) 1732 cm^{-1}; mp: 48°C, ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 6.36 (s, 2H, C<u>H</u>=C<u>H</u>), 4.94 (s, 2H, C<u>H</u>-O-C<u>H</u>), 2.56-2.45 (m, 1H, C<u>H</u>-CO-CH), 2.31-2.29 (m, 2H, C<u>H</u>$_2$-CH_2-CH_2), 2.27-2.20 (m, 2H, CH_2-CH_2-C<u>H</u>$_2$),2.07-1.97 (m, 2H, CH_2-C<u>H</u>$_2$-CH_2), 1.49-1.40 (m, 1H, CH-CO-C<u>H</u>).

12-Oxa-tricyclo[4.4.1.12,5]dodec-3-en-11-one (3.35c).

A mixture of $Fe_2(CO)_9$ (1.2 mmol), 2,7 dibromocycloheptanone (1 mmol) and furan (12 mL) was heated at reflux for 62h and then the mixture was cooled to rt.
The resulting precipitate was removed by filtration through a pad of Celite and the filtrate was concentrated under vacuum to give a yellow oil.
The crude product was purified by flash chromatography (eluent Diethyl Ether : Petroleum Ether 1:2) to give **3.35c** as a yellow oil in 50% yield.

R_f: 0.35 (Diethyl Ether : Petroleum Ether 1:2) IR (CCl_4) 1750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 6.23 (s, 2H, C<u>H</u>=C<u>H</u>), 4.65 (s, 2H, C<u>H</u>-O-C<u>H</u>), 2.47 (t, J= 1.2, 1H, C<u>H</u>-CO-CH), 2.45 (t, J= 1.2, 1H, CH-CO-C<u>H</u>), 1.99-1.90 (m, 2H, CH_2-CH_2-C<u>H</u>$_2$), 1.85-1.76 (m, 2H, CH_2-CH_2-C<u>H</u>$_2$), 1.73-1.66 (m, 2H, CH_2-CH_2-C<u>H</u>$_2$), 1.42-1.33 (m, 2H, CH_2-CH_2-C<u>H</u>$_2$); ^{13}C-NMR (106.6 MHz): δ_C 209.9 (<u>C</u>=O), 134.0 (H<u>C</u>=<u>C</u>H), 82.9 (<u>C</u>H-O-<u>C</u>H) , 54.1 (CH_2-<u>C</u>H_2-<u>C</u>H_2-CH_2), 29.4 (<u>C</u>H_2-CH_2-CH_2-CH_2), 26.7 (CH_2-CH_2-CH_2-<u>C</u>H_2).

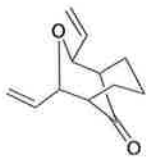
2,4-Divinyl-3-oxa-bicyclo[3.2.1]octan-8-one (3.40a).



To a solution of **3.35a** (1 mmol) in dry CH_2Cl_2 (8 mL) and Grubbs' cat. I gen. (5% mol) dissolved in dry CH_2Cl_2 (8 mL) ethylene was added under pressure (500 psi). The mixture was stirred for 3h at rt, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent CH_2Cl_2) to give **3.40a** as a yellow oil in 90% yield.

Rf 0.35 in DCM; IR (CCl_4) 1755, 1549 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.97-5.90 (ddd, 2H, J_{cis}=10.4, J_{trans}=17.6, J_{AB}=7.2, CH_2=C<u>H</u>), 5.20-5.16 (dt, 2H, J_{trans}=17.2, $J_{cis/trans}$= 1.2, C<u>H</u>$_2$=CH), 5.5.10-5.08 (dt, 2H, J_{cis} =10.4, $J_{cis/trans}$=1.2, C<u>H</u>$_2$=CH), 4.50-4.48 (m, 2H, C<u>H</u>-O-C<u>H</u>); 2.32-2.30 (m, 2H, C<u>H</u>-CO-C<u>H</u>), 2.10-1.97 (m, 4H, C<u>H</u>$_2$-C<u>H</u>$_2$); ^{13}C-NMR(106.6 MHz): δ_C= 213.7 (<u>C</u>=O), 137.8 (CH_2=<u>C</u>H), 117.6 (<u>C</u>H_2=CH), 88.5 (<u>C</u>H-CO-<u>C</u>H), 49.6 (<u>C</u>H-CO-<u>C</u>H), 22.3 (<u>C</u>H_2-<u>C</u>H_2).

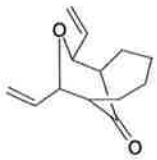
2,4-Divinyl-3-oxa-bicyclo [3.3.1]nonan-9-one (3.40b).



To a solution of **3.35b** (1 mmol) in dry CH_2Cl_2 (8 mL) and Grubbs' cat. I gen. (5% mol) dissolved in dry CH_2Cl_2 (8 mL), ethylene was added under pressure (500 psi). The mixture was stirred for 3h at rt and then filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent CH_2Cl_2) to give **3.40b** as yellow oil in 77% yield.

Rf 0.33 in DCM; IR (CCl_4) 1753, 1546 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.90-5.81 (m, 2H, J_{trans}=17.2, J_{cis}= 10.4, $J_{A/B}$=6.8, CH_2=C<u>H</u>), 5.16 (dt, 2H, J_{trans}=17.2, $J_{cis/trans}$=1.2, C<u>H</u>$_2$=CH), 5.05 (dt, 2H, J_{cis}=10.4, $J_{cis/trans}$=1.2, C<u>H</u>$_2$=CH), 4.56 (m, 2H, C<u>H</u>-O-C<u>H</u>), 2.47 (d, 2H, J=2.4, C<u>H</u>-CO-C<u>H</u>), 2.44-2.31 (m, 1H, C<u>H</u>$_2$-CH_2-CH_2), 2.10-2.05 (m, 2H, CH_2-C<u>H</u>$_2$-CH_2), 1.97-1.88 (m, 2H, CH_2-CH_2-C<u>H</u>$_2$), 1.63-1.58 (m, 1H, C<u>H</u>$_2$-CH_2-CH_2); ^{13}C-NMR(106.6 MHz): δ_C= 213.7 (<u>C</u>=O), 138.8 (CH_2=<u>C</u>H), 116.1(<u>C</u>H_2=CH), 82.8 (<u>C</u>H-CO-CH), 52.0 (<u>C</u>H-CO-<u>C</u>H), 34.1(<u>C</u>H_2-CH_2-<u>C</u>H_2), 17.6 (CH_2-<u>C</u>H_2-CH_2).

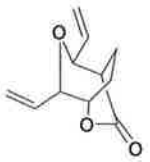
2,4-Divinyl-3-oxa-bicyclo[3.3.1]nonan-9-one (3.40c).



To a solution of **3.35c** (1 mmol) in dry CH_2Cl_2 (8 mL) and Grubbs' cat. I gen. (5% mol) dissolved in dry CH_2Cl_2 (8 mL), ethylene was added under pressure (>500 psi). The mixture was stirred for 24h at 40°C, then filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent CH_2Cl_2) to give **3.40c** as a yellow oil in 8% yield.

Rf 0.35 in CH_2Cl_2; IR (CCl_4) 1754, 1540 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): 5.84-5.75 (m, 2H, J_{trans}=17.2, J_{cis}= 10.4, $J_{A/B}$= 6.8, CH_2=C<u>H</u>), 5.24 (dt, 2H, J_{trans}=17.2, $J_{cis/trans}$=1.2, C<u>H</u>$_2$=CH), 5.13 (dt, 2H, J_{cis}=10.4, $J_{cis/trans}$=1.2, C<u>H</u>$_2$=CH), 4.36 (t, J=6.4, 2H, C<u>H</u>-O-C<u>H</u>),2.63-2.59 (m, 2H, C<u>H</u>$_2$-CH_2-CH_2-CH_2), 1.90-1.78 (m, 4H, CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2), 1.60-1.54 (m, 4H, CH_2-CH_2-CH_2-C<u>H</u>$_2$); ^{13}C-NMR(106.6 MHz): δ_C= 211.3 (<u>C</u>=O), 137.6 (CH_2=<u>C</u>H), 116.2 (<u>C</u>H_2=CH), 81.7 (<u>C</u>H-CO-<u>C</u>H), 53.5 (<u>C</u>H-CO-<u>C</u>H), 29.7 (CH_2-<u>C</u>H_2-<u>C</u>H_2-CH_2), 28.1 (<u>C</u>H_2-CH_2-CH_2-CH_2), 25.6 (CH_2-CH_2-CH_2-<u>C</u>H_2).

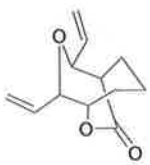
2,4-Divinyl-3,6-dioxa-bicyclo[3.2.2]nonan-7one (3.41a).



To a solution of compound **3.40a** (1 mmol) dissolved in CH_3CN/10% H_2O (20/2 mL) was added Oxone® (5 mmol) at rt. After 2 days, the mixture was concentrated under reduced pressure. The resulting white solid was dissolved in water and the product was extracted with CH_2Cl_2 (3 X 20 mL). The organic layer was concentrated under reduced pressure to give **3.41a** as yellow oil in 91% yield.

IR (CCl_4) 1765, 1547 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.96-5.88 (ddd, 2H, J_{cis} =10.8, J_{trans}=17.2, J_{AB}=6.4, CH_2=C<u>H</u>), 5.32-5.24 (dt, 2H, J_{trans}=17.2, $J_{cis/trans}$= 1.2, C<u>H</u>$_2$=CH), 5.17-5.14 (dd, 2H, J_{cis} =10.4, $J_{cis/trans}$=1.2, C<u>H</u>$_2$=CH), 4.46-4.45 (d, 1H, J=6.8, C<u>H</u>-O-CO), 3.97-3.90 (dd, 2H, J=1.2, C<u>H</u>-O-C<u>H</u>), 2.88-2.86 (t, 1H, J=3.2, C<u>H</u>-CO), 2.30-2.21 (m, 1H,C<u>H</u>$_2$-CH$_2$), 2.07-2.02 (m, 2H, C<u>H</u>$_2$-CH$_2$), 1.97-1.89 (m, 1H, C<u>H</u>$_2$-CH$_2$); ^{13}C-NMR(106.6 MHz): δ_C= 171.2 (<u>C</u>=O), 136.6 (<u>C</u>H=CH$_2$), 136.5 (<u>C</u>H=CH$_2$), 117.3 (<u>C</u>H$_2$=CH), 116.69 (<u>C</u>H$_2$=CH), 81.5 (O-C<u>H</u>-CH-O), 81.3 (O-<u>C</u>H-CH-CO), 78.2 (C<u>H</u>-O-CO), 48.5 (C<u>H</u>-CO), 25.0 (O-<u>C</u>H-CH$_2$), 23.1 (<u>C</u>H$_2$-CH-CO). HRMS found:[M+] 194.0948, $C_{11}H_{14}O_3$ requires: 194.0943; m/z: 194 (100%, [M+]).

2,4-Divinyl-3,9-dioxa-bicyclo[3.3.2]decan-10one (3.41b).

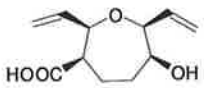


To a solution of compound **3.40b** (1 mmol) dissolved in CH_3CN/10% H_2O (20/2 mL) was added Oxone® (5 mmol) at rt. After 2 days the mixture was concentrated under

reduced pressure. The resulting white solid was dissolved in water and the product was extracted with CH_2Cl_2 (3 X 20 mL). The organic layer was concentrated under reduced pressure to give **3.41b** as yellow oil in 40% yield.

IR (CCl_4) 1758, 1542 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 6.08-5.97 (m, 2H, J_{trans}=17.2, J_{cis}=10.8, J_{AB}=6.8, CH_2=C<u>H</u>), 5.33-5.27 (dt, 2H, J=1.2, C<u>H</u>$_2$=CH), 5.20-5.15 (t, 2H, J=11.2, J=0.8, C<u>H</u>$_2$=CH), 4.43-4.41 (m, 1H, C<u>H</u>-O-CO), 4.30-4.28 (dt, 1H, J=8, J=0.8, C<u>H</u>-O-CO), 4.23-4.21 (dt, 1H, J=7.6, J=1.2, C<u>H</u>-O-C<u>H</u>), 3.26-3.23 (m, 1H, C<u>H</u>-CO), 2.40-2.28 (m, 1H, C<u>H</u>$_2$-CH_2), 2.08-2.036 (m, 2H, C<u>H</u>$_2$-CH_2), 1.92-1.87 (m, 2H, C<u>H</u>$_2$-CH_2), 1.84-1.77 (m, 1H, C<u>H</u>$_2$-CH_2); ^{13}C-NMR(106.6 MHz): δ_C= 173.8 (<u>C</u>=O), 138.2 (<u>C</u>H=CH_2), 137.6 (<u>C</u>H=CH_2), 116.8 (<u>C</u>H$_2$=CH), 116.04 (<u>C</u>H$_2$=CH), 77.8 (O-C<u>H</u>-CH-O), 77.6 (O-<u>C</u>H-CH-CO), 75.9 (C<u>H</u>-O-CO), 51.8 (C<u>H</u>-CO), 31.6(O-<u>C</u>H-CH_2), 26.1 (CH-<u>C</u>H$_2$-CO), 19.4 (CH_2-<u>C</u>H$_2$-CH_2). HRMS found:[M+] 208.1096, $C_{12}H_{16}O_3$ requires: m/e: 208.1099 ; m/z: 208 (100%, [M+]).

6-Hydroxy-2,7-divinyl-oxepane-3-carboxylic acid (3.42a).

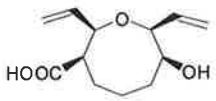


To a solution of **3.41a** (1 mmol) in MeOH (4 mL), KOH 3N (6.6 mmol) was stirred for 24h at rt. Volatiles were removed under vacuum, water and an equimolar amount of HCl 1.2N (7.7 mmol) were added adjusting the pH to about 3. Et_2O (3 X 15mL) was added and the two phases were separate. The combinated organic layers were washed with brine, dried with Na_2SO_4 and evaporated to yield **3.42a** in 92%. The product was crystallized from $CHCl_3$ to give white needles.

IR (CCl_4) 2753, 1549 cm^{-1}; mp: 95°C ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.90-5.75 (m, 2H, CH_2=C<u>H</u>), 5.36-5.31 (dd, 2H, J_{trans}=17.2, $J_{cis/trans}$= 1.2, C<u>H</u>$_2$=CH), 5.21-5.15 (dt, 2H, J_{cis} =10.4, $J_{cis/trans}$=1.2, C<u>H</u>$_2$=CH), 4.47-4.44 (t, 1H, J=6, C<u>H</u>-O-CH), 4.05-4.04 (m, 1H,

CH-O-C<u>H</u>), 3.85-3.83 (t, 1H, J=3.2, C<u>H</u>-OH), 2.97-2.92 (m, 1H, C<u>H</u>-COOH),2.08-1.94 (m, 2H, C<u>H</u>$_2$-CH$_2$), 1.85 (m, 1H, CH$_2$-C<u>H</u>$_2$), 1.62 (m, 1H, CH$_2$-C<u>H</u>$_2$); ^{13}C-NMR(106.6 MHz): δ_C= 176.2 (<u>C</u>OOH), 135.9 (CH$_2$=<u>C</u>H), 134.6 (CH$_2$=<u>C</u>H), 117.7 (<u>C</u>H$_2$=CH), 116.8 (<u>C</u>H$_2$=CH), 80.9 (<u>C</u>H-O-CH), 78.5 (CH-O-<u>C</u>H), 71.5 (<u>C</u>H-COOH), 49.9 (<u>C</u>H-OH), 33.7 (<u>C</u>H$_2$-CH$_2$), 19.3 (<u>C</u>H$_2$-CH$_2$). HRMS found: [M+Na$^+$] 235.0953, $C_{11}H_{16}NaO_4$ requires 235.0946, m/z: 212 (100%, [M+Na$^+$]).

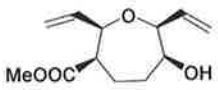
6-Hydroxy-2,8-divinyl-oxocane-3-carboxylic acid (3.42b).



To a solution of **3.41b** (1 mmol) in MeOH (4 mL), KOH 3N (6.6 mmol) was stirred for 24h at rt. Volatiles were removed under reduced pressure, water and an equimolar amount of HCl 1.2N (7.7 mmol) were added adjusting the pH to about 3. Et$_2$O (3 X 15mL) was added and the two phases were separate. The combined organic layers were washed with brine, dried with Na$_2$SO$_4$ and evaporated to yield **3.42b** in 80%. The product was crystallized from CHCl$_3$ to give white needles.

IR (CCl$_4$) 2750, 1555 cm^{-1}; mp: 110°C ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H= 5.89-5.78 (m, 2H, CH$_2$=C<u>H</u>), 5.36-5.34 (m, 1H, C<u>H</u>$_2$=CH), 5.31-5.03 (m, 1H, C<u>H</u>$_2$=CH), 5.21-5.16 (m, 2H, C<u>H</u>$_2$=CH), 4.40-4.37 (t, 1H, J=5.2, C<u>H</u>-O-CH), 4.09-4.04 (m,1H, CH-O-C<u>H</u>), 3.73-3.71 (m, 1H, C<u>H</u>-OH), 3.07-3.02 (m, 1H, C<u>H</u>-COOH), 2.08-1.94 (m, 2H, C<u>H</u>$_2$-CH$_2$-CH$_2$), 1.92-1.83 (m,1H, C<u>H</u>$_2$-CH$_2$-CH$_2$), 1.74-1.66 (m, 1H, CH$_2$-CH$_2$-C<u>H</u>$_2$), 1.62-1.56 (m, 1H, C<u>H</u>$_2$-CH$_2$-CH$_2$), 1.46-1.37 (m, 1H, C<u>H</u>$_2$-CH$_2$-CH$_2$). ^{13}C-NMR(106.6 MHz): δ_C= 178.2 (<u>C</u>OOH), 135.9 (CH$_2$=<u>C</u>H), 134.0 (CH$_2$=<u>C</u>H), 117.8 (<u>C</u>H$_2$=CH), 116.4 (<u>C</u>H$_2$=CH), 79.6 (<u>C</u>H-O-<u>C</u>H), 70.9 (<u>C</u>H-OH), 45.1(<u>C</u>H-COOH), 32.6 (<u>C</u>H$_2$-CH$_2$-CH$_2$), 25.2 (CH$_2$-CH$_2$-<u>C</u>H$_2$), 17.9 (CH$_2$-<u>C</u>H$_2$-CH$_2$). HRMS found: [M+Na$^+$] 249.1115, $C_{12}H_{18}NaO_4$ requires 249.1103, m/z: 249 (100%, [M+Na$^+$]).

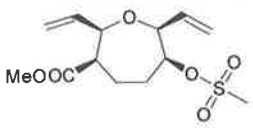
6-Hydroxy-2,7-divinyl-oxepane-3-carboxylic acid methyl ester (3.43).



To a solution of **3.42a** (1 mmol.) in MeOH (8 mL), aectylchloride (0.3 mmol) was added and stirred for 24h. The solution was dried under reduced pressure. Water was added and the product was extracted with CH_2Cl_2 (3 X 10 mL). The crude product was purified by flash chromatography (eluent $CHCl_3$:Ethyl Acetate 8:2) to give **3.43** as a yellow oil in 29% yield and the lactone **3.41a** in 56% yield.

Rf 0.41 in 8:2 $CHCl_3$:EtOAc; IR (CCl_4) 1744, 1590 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.20-5.84 (m, 1H, J=15.6, J=10.8, J=4.8, CH_2=C<u>H</u>), 5.76-5.68 (m, 1H, J=16.8, J=10.4, J=6.4, CH_2=C<u>H</u>), 5.32-5.28 (dt, 2H, J=12.0, J=1.6, C<u>H</u>$_2$=CH), 5.28-5.24 (dt, 1H, J=12.0, J=1.2), 5.17-5.10 (m, 2H, C<u>H</u>$_2$=CH), 4.48-4.47 (t, 1H, J=6.4, CH-O-C<u>H</u>), 4.02-4.01 (d, 1H, J=4.8, C<u>H</u>-O-CH), 3.78 (s, 1H, C<u>H</u>-OH), 3.57 (s, 3H, O-C<u>H</u>$_3$), 2.94-2.90 (m, 1H, J=9.2, J=6, J=2.4, C<u>H</u>-COOCH$_3$), 2.05-1.98 (m, 1H,C<u>H</u>$_2$-CH$_2$), 1.96-1.89 (m, 1H, C<u>H</u>$_2$-CH$_2$), 1.85-1.78 (m, 1H, CH$_2$-C<u>H</u>$_2$), 1.56-1.47 (m, 1H, CH$_2$-C<u>H</u>$_2$); ^{13}C-NMR(106.6 MHz): δ_C= 173.3 (COOH), 136.5 (CH$_2$=<u>C</u>H), 134.9 (CH$_2$=<u>C</u>H), 117.5 (<u>C</u>H$_2$=CH), 116.1 (<u>C</u>H$_2$=CH), 80.0 (<u>C</u>H-O-CH), 78.5 (CH-O-<u>C</u>H), 71.5 (<u>C</u>H-OH), 55.8 (O-<u>C</u>H$_3$), 50.2 (<u>C</u>H-COOH), 34.9 (<u>C</u>H$_2$-CH$_2$), 18.9 (<u>C</u>H$_2$-CH$_2$). HRMS found:[M-H]$^-$ 225.1207, $C_{12}H_{17}O_4$ requires: 225.1205; m/z: 225 (100%, [M-H]$^-$).

6-Methanesulfonoxyloxy-2,7-divinyl-oxepane-3-carboxylic acid methyl ester (3.43e).

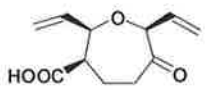


To a solution of Methanesulfonylchloride (0.78 mmol,) and NEt_3 (0.78 mmol,) in CH_2Cl_2 (3 mL), **3.43** dissolved in CH_2Cl_2 (3 mL) was added dropwise at 0°C. The solution was

stirred for 12h at rt. The product was dried under reduced pressure and the crude was purified by flash chromatography (eluent CH_2Cl_2) to give **3.43e** as a yellow oil in 61% yield .

Rf 0.38 in CH_2Cl_2; IR (CCl_4) 1746, 1585 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.86-5.72 (m, 2H, CH_2=C<u>H</u>), 5.36-5.29 (dt, 1H, J=18.8, J=1.6, C<u>H</u>$_2$=CH), 5.29-5.24 (dt, 1H, J=18.4, J=1.2, C<u>H</u>$_2$=CH), 5.22-5.19 (dt, 1H, J=12.0, 1.2 C<u>H</u>$_2$=CH), 5.14-5.10 (dt, 1H, J=12, J=1.2 C<u>H</u>$_2$=CH), 4.87-4.85 (t, 1H, J=2.8, CH-O-C<u>H</u>) 4.40-4.37 (t, 1H, J=6.8, CH-O-C<u>H</u>), 4.10-4.08 (m, 1H, C<u>H</u>-OH), 3.60 (s, 3H, O-C<u>H</u>$_3$), 2.96 (s, 3H, SO_2-C<u>H</u>$_3$), 2.93-2.88 (m, 1H, J=10, J=7.2, J=2.8, CH-COOH), 2.38-2.32 (m, 1H, C<u>H</u>$_2$-CH_2), 2.23-2.13 (m, 1H, C<u>H</u>$_2$-CH_2), 1.87-1.80 (m, 1H, CH_2-C<u>H</u>$_2$), 1.74-1.65 (m, 1H, CH_2-C<u>H</u>$_2$). HRMS found:$[M+H]^+$ 305.0979, $C_{13}H_{21}O_6S$ requires: 305.0981; m/z: 305 (100%, :$[M+H]^+$).

6-Oxo-2,7-divinyl-oxepane-3-carboxylic acid (3.44a).

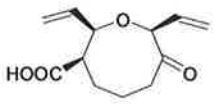


A Solution of **3.42a** (1 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with Dess-Martin periodane (1.2 mmol). After stirring at r.t. for 30 min, $Na_2S_2O_3$ (1.5 mL) and of saturated aqueous $NaHCO_3$ (1.5 mL) were added and the mixture was stirred for 1 h. The organic layer were combined, dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel (eluent $CHCl_3$:MeOH 9:1) to give **3.44a** as a yellow oil in 54% yield.

Rf 0.55 in 9:0.5 $CHCl_3$:MeOH; IR (CCl_4) 2746, 1768, 1549 cm^{-1}^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 11.2 (s, 1H, COO<u>H</u>), 6.06-6.14 (dq, 1H, J=24.4, J=17.6, J=7.2, CH_2=C<u>H</u>), 5.73-5.82 (dq, 1H, J=15.2, J=10.4, J=4.4, CH_2=C<u>H</u>), 5.53-5.48 (dt, 1H, J=17.6, J=1.2, C<u>H</u>$_2$=CH), 5.37-5.32 (dt, 1H, J=17.2, J=1.2, C<u>H</u>$_2$=CH), 5.27-5.24 (dt, 1H, J=10.8, J=1.6, C<u>H</u>$_2$=CH), 5.27-5.19 (dt, 1H, J=10.4, J=1.6, C<u>H</u>$_2$=CH), 4.35-4.37 (m, 1H, J=4.4, J=2,

C<u>H</u>-O-CH), 4.00-4.02 (m, 1H, J=3.6, J=2, CH-O-C<u>H</u>), 3.26-3.53 (m, 1H, C<u>H</u>$_2$-C=O), 2.88-2.89 (m, 1H, C<u>H</u>-COOH), 2.24-2.40 (m, 2H, C<u>H</u>$_2$-CH$_2$), 1.65-1.82 (m,1H, C<u>H</u>$_2$-C=O); ^{13}C-NMR(106.6 MHz): δ_C= 212.3 (<u>C</u>=O), 136.2 (CH$_2$=<u>C</u>H), 131.8 (CH$_2$=<u>C</u>H), 118.0 (<u>C</u>H$_2$=CH), 116.4 (<u>C</u>H$_2$=CH), 87.2 (<u>C</u>H-O-CH), 82.1(<u>C</u>H-O-CH), 47.7 (<u>C</u>H-COOH) , 36.7 (<u>C</u>H$_2$-CH$_2$) , 26.0 (<u>C</u>H$_2$-CH$_2$). HRMS found:[M-H]$^-$ 209.0811, $C_{11}H_{13}O_4$ requires: 209.0814; m/z: 209 (100%, :[M-H]$^-$).

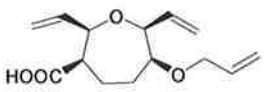
7-Oxo-2,8-divinyl-oxocane-3-carboxylic acid (3.44b).



A Solution of **3.42b** (1.57 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with Dess-Martin periodane (1.88 mmol). After stirring at rt for 30 min, $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (2 mL) were added and the mixture was stirred for 1 h. The organic layer were combined, dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel (eluent $CHCl_3$:MeOH 9:1) to give **3.44b** as a yellow oil in 40% yield.

Rf 0.53 in 9:0.5 $CHCl_3$:MeOH; IR (CCl_4) 2753, 1772, 1545 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.80-5.67 (m, 2H, CH$_2$=C<u>H</u>), 5.51-5.42 (m, 2H C<u>H</u>$_2$=CH), 5.267-5.22 (m, 2H, C<u>H</u>$_2$=CH), 4.44 (t, 1H, J= 5.2, CH-O-C<u>H</u>), 4.21-4.19 (m, 1H, C<u>H</u>-O-CH), 2.87-2.81 (m, 1H, C<u>H</u>-COOH), 2.55-2.52 (m, 1H, C<u>H</u>$_2$-C=O), 2.15-2.06 (m, 2H, CH$_2$-C<u>H</u>$_2$-CH$_2$), 1.73-1.68 (m, 1H, C<u>H</u>$_2$-C=O), 1.57-1.45 (m, 2H, C<u>H</u>$_2$-CH$_2$-CH$_2$). δ_C= 216.3 (<u>C</u>=O), 175.0 (<u>C</u>OOH), 133.0 (CH$_2$=<u>C</u>H), 132.2 (CH$_2$=<u>C</u>H), 118.7 (<u>C</u>H$_2$=CH), 117.6 (<u>C</u>H$_2$=CH), 85.9 (<u>C</u>H-O-CH), 80.6 (<u>C</u>H-O-CH), 47.4 (<u>C</u>H-COOH) , 38.1 (CH$_2$-CH$_2$-<u>C</u>H$_2$-C=O), 28.5 (CH$_2$-CH$_2$-<u>C</u>H$_2$), 23.5 (<u>C</u>H$_2$-CH$_2$-CH$_2$). HRMS found:[M-H]$^-$ 223.0966, $C_{12}H_{15}O_4$ requires: 223.0970; m/z: 223 (100%, :[M-H]$^-$).

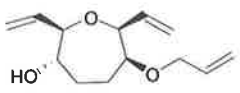
6-Allyloxy-2,7-divinyl-oxepane-3-carboxylic acid (3.46).



To a solution of NaH (4 mmol) in dry THF (10 mL) at 0°C **3.42a** (1mmol) dissolved in dry THF (7 mL) was added dropwise and stirred for 1h. Allylbromide (1.2 mmol) was added and the solution stirred for 12h. The reaction was concentrated under reduced pressure and then H_2O (3 mL) was added. The H_2O layer was washed with CH_2Cl_2 (3 X 3 mL). HCl 3M (3 mmol) was added to the H_2O phase and the product was extracted with CH_2Cl_2 (3 X 3 mL) .The organic layer was dried under Na_2SO_4 and concentrated under vacuum to give **3.46** as a colourless oil in 65% yield.

Rf 0.57 in 9:1 $CHCl_3$:MeOH; IR (CCl_4) 2750, 1765, 1540 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 6.03-5.95 (m, 1H, CH_2=C<u>H</u>), 5.91-5.83 (m, 2H, CH_2=C<u>H</u>), 5.41-5.29 (m, 2H, C<u>H</u>$_2$=CH), 5.25-5.17 (m, 4H, C<u>H</u>$_2$=CH), 4.33-4.30 (m, 1H, C<u>H</u>-O-CH), 4.15-4.10 (ddt, 1H, J=5.2, J=1.2, CH-C<u>H</u>$_2$-O), 4.06-4.03 (m, 1H, C<u>H</u>-O), 3.97-3.92 (ddt, 1H, J=6.0, J=1.2, CH-C<u>H</u>$_2$-O), 3.74-3.72(m, 1H, CH-O-C<u>H</u>), 2.99-2.95 (m, 1H, C<u>H</u>-COOH), 2.23-2.15 (m, 1H, C<u>H</u>$_2$-CH$_2$), 2.14-2.08 (m, 1H, C<u>H</u>$_2$-CH$_2$), 2.05-1.97 (m, 1H, CH$_2$-C<u>H</u>$_2$), 1.88-1.81 (m, 1H, C<u>H</u>$_2$-CH$_2$); ^{13}C-NMR(106.6 MHz): δ_C= 176.9 (<u>C</u>OOH), 136.4 (CH$_2$=<u>C</u>H), 135.5 (CH$_2$=<u>C</u>H), 134.7 (CH$_2$=<u>C</u>H), 117.3 (<u>C</u>H$_2$=CH) , 116.8 (<u>C</u>H$_2$=CH), 115.9 (<u>C</u>H$_2$=CH), 83.1 (<u>C</u>H-O), 79.2 (<u>C</u>H-O-CH), 78.7 (<u>C</u>H-O-CH), 70.4 (CH-<u>C</u>H$_2$-O), 50.6 (<u>C</u>H-COOH), 29.0 (<u>C</u>H$_2$-CH$_2$), 21.0 (CH$_2$-<u>C</u>H$_2$). HRMS found:[M-H]$^-$ 251.1284, $C_{14}H_{19}O_4$ requires: 251.1283; m/z: 251 (100%, [M-H]$^-$).

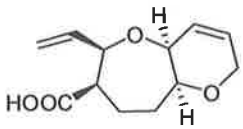
6-Allyloxy-2,7-divinyl-oxepan-3-ol (3.47).



To a solution of **3.46** (1 mmol) in CH_2Cl_2 (20 mL) and THF (10 mL) was added EDC (1.5 mmol) at rt, followed by addition of a solution of 2-mercaptopyridine-N-oxide (1.5 mmol) dissolved in CH_2Cl_2 (2 mL) under dark conditions. After stirring the solution for 2h, Oxygen gas was added and the mixture was stirred at rt for 1.5h under 45W fluorescent light. PPh_3 (0.5 mmol) was added to the reaction and the resulting mixture was stirred for 1h. Saturated NH_4Cl (4 mL) was added to the mixture and extracted with CH_2Cl_2 (3 X 3 mL). The organic layer was washed with brine (4 mL), dried with $MgSO_4$ and concentrated under vacuum. The product was purified by silica gel ($CHCl_3$:EtOAc 2:2) to give **3.47** as a yellow oil in 49% yield.

Rf 0.24 in 2:2 $CHCl_3$:EtOAc; IR (CCl_4) 1544 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO): δ_H= 5.94-5.85 (m, 2H, CH_2=C<u>H</u>), 5.84-5.75 (m, 1H, CH_2=C<u>H</u>), 5.29-5.09 (m, 6H, C<u>H</u>$_2$=CH), 4.04-4.01 (m, 1H,C<u>H</u>-O-CH), 3.99-3.98 (m, 1H, CH-C<u>H</u>$_2$-O), 3.86-3.81 (m, 1H, CH-C<u>H</u>$_2$-O), 3.60-3.55 (m, 3H, CH-O-C<u>H</u>, C<u>H</u>-OH, C<u>H</u>-O-CH_2), 2.22-2.15 (m, 1H, C<u>H</u>$_2$-CH_2), 1.98-1.90 (m,1H, C<u>H</u>$_2$-CH_2), 1.80-1.75 (m,1H, CH_2-C<u>H</u>$_2$), 1.52-1.50 (m, 1H, CH_2-C<u>H</u>$_2$); ^{13}C-NMR (106.6 MHz): δ_C= 137.7 (CH_2=<u>C</u>H), 136.4 (CH_2=<u>C</u>H), 135.2 (CH_2=<u>C</u>H), 116.9 (<u>C</u>H$_2$=CH), 116.6 (<u>C</u>H$_2$=CH), 115.2 (<u>C</u>H$_2$=CH), 87.1(<u>C</u>H-O-CH), 85.5 (<u>C</u>H-O-CH), 79.1 (<u>C</u>H-O-CH_2), 74.5 (<u>C</u>H-OH), 70.4 (O-<u>C</u>H$_2$-CH), 28.6 (<u>C</u>H$_2$-CH_2), 24.9 (CH_2-<u>C</u>H$_2$). HRMS found:$[M+Na]^+$ 247.1312, $C_{13}H_{20}NaO_3$ requires:247.1310; m/z: 247 (100%, $[M+Na]^+$).

6-Vinyl-4a,6,7,8,9,9a-hexahydro-2*H*-1,5-dioxa-benzocycloheptene-7-carboxylic acid (3.48).

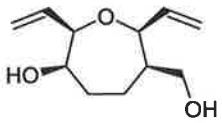


To a solution of Grubbs' catalyst I generation (15% mol) in dry CH_2Cl_2 (32 mL), **3.46** (1 mmol) dissolved in dry CH_2Cl_2 (72 mL) was added dropwise. The solution was stirred for

6h. The reaction was filtered and dried under reduced pressure. The crude was purified by flash chromatography (eluent $CHCl_3$:EtOAc 10:1) to give **3.48** as colourless oil in 65% yield.

Rf 0.66 $CHCl_3$:EtOAc 10:1; IR (CCl_4) 2758, 1772, 1544 cm^{-1} ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.97-5.94 (m, 1H, J_{cis}=10, J=2.4, CH_2=C<u>H</u>), 5.90-5.82 (m, 2H, C<u>H</u>=C<u>H</u>), 5.31-5.27 (d, 1H, J_{trans}=16, C<u>H$_2$</u>=CH), 5.15-5.12 (d, 1H, J_{cis}=10.8, C<u>H$_2$</u>=CH), 4.27-4.13 (m, 2H, CH-C<u>H$_2$</u>-O), 4.05-4.01 (m, 1H, O-C<u>H</u>-CH$_2$), 3.76-3.75 (m, 1H, J=2, O-C<u>H</u>-CH=CH$_2$), 3.70-3.68 (m, 1H, J=4, J=2.8, O-C<u>H</u>-CH=CH), 2.85-2.81 (m, 1H, C<u>H</u>-COOH), 2.30-1.80 (m, 4H, C<u>H$_2$</u>-C<u>H$_2$</u>); ^{13}C-NMR(106.6 MHz): δ_C= 174.1 (<u>C</u>OOH), 134.6 (<u>C</u>H=CH), 130.0 (CH_2=<u>C</u>H), 122.7 (<u>C</u>H=CH), 115.2 (<u>C</u>H$_2$=CH), 79.7 (O-<u>C</u>H-CH$_2$), 74.9 (CH-O-<u>C</u>H), 74.8 (<u>C</u>H-O-CH), 64.2 (CH-C<u>H$_2$</u>-O), 49.3 (<u>C</u>H-COOH), 30.9 (<u>C</u>H$_2$-CH$_2$), 27.7 (CH$_2$-<u>C</u>H$_2$). HRMS found:$[M+Na]^+$ 246.0865, $C_{12}H_{15}NaO_4$ requires:246.0868; m/z: 246 (100%, $[M+Na]^+$).

6-Hydroxymethyl-2,7-divinyl-oxepan-3-ol (3.49).



To a solution of **3.41a** (1 mmol) in THF (7 mL), $LiAlH_4$ (2 mmol) was added. The mixture was stirred for 2h to reflux. After being cooled to rt, a solution 15% KOH was added and the mixture was extracted with EtOAc (3 X 3 mL). The crude was purified by silica gel (eluent CH_2Cl_2:EtOAc 1:1) to give **3.49** in 69% yield.

Rf 0.30 in CH_2Cl_2:EtOAc 1:1; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H= 5.92-5.76 (m, 2H, J_{trans}=17.2, J_{cis}=12.8, J_{AB}=6.8, CH_2=C<u>H</u>), 5.37-5.33 (dt, 1H, J_{cis}= 12.8, J=1.6, C<u>H$_2$</u>=CH), 5.32-5.28 (dt, 1H, J_{trans}=17.2, J=1.6, C<u>H$_2$</u>=CH), 5.19-5.15 (m, 2H, J=10.4, J=1.6, C<u>H$_2$</u>=CH), 4.32-4.29 (m, 1H, C<u>H</u>-O-CH), 4.08-4.03 (m, 1H, CH-O-C<u>H</u>), 3.82 (s, O<u>H</u>),

3.58-3.44 (m, 2H, C$\underline{H}_2$-OH), 2.11-1.97 (m, 2H, C$\underline{H}_2$-CH_2), 1.83-1.74 (m, 1H, CH_2-C$\underline{H}_2$), 1.66-1.56 (m, 1H, CH_2-C$\underline{H}_2$); ^{13}C-NMR(106.6 MHz): δ_C= 136.7 (CH_2=$\underline{C}$H), 136.0 (CH_2=$\underline{C}$H), 116.7 ($\underline{C}H_2$=CH), 116.1 ($\underline{C}H_2$=CH), 80.9 ($\underline{C}$H-O-CH), 80.5 (CH-O-$\underline{C}$H), 71.9 ($\underline{C}$H-OH), 64.3 ($\underline{C}H_2$-OH), 44.5 ($\underline{C}$H-CH_2-OH), 34.0 ($\underline{C}H_2$-CH_2), 19.9 ($\underline{C}H_2$-CH_2).

Materials and Methods for Chapter 4.

General Methods.

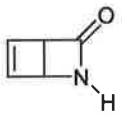
^{1}H and ^{13}C NMR Spectra were recorded on a 200 or a 400 MHz spectrometer at ambient temperatures. ^{1}H NMR spectral assignments are supported by ^{1}H-^{1}H COSY and ^{13}C-^{1}H COSY where necessary. For ^{1}H NMR recorded in $CDCl_3$ chemical shifts (δH) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet, d, doublet, t, triplet, dd, doublet of doublets, dt, doublet of triplets, tt, triplet of triplets, m, multiplet and br, broad. Coupling constants (J) were recorded in Hertz (Hz) to the nearest 0.5 Hz. Carbon spectra are supported by DEPT analysis where necessary. Infrared (IR) spectra were recorded as thin films between NaCl plates. Absorption maximum (υ_{max}) was reported in wavenumbers (cm^{-1}) and only selected peaks are reported. The following abbreviations are used: w, weak, m, medium, s, strong and br, broad. High resolution mass spectra were obtained on a Waters Micro mass LCT and low resolution mass spectra were recorded on Waters Micro mass Quattro LCMS spectrometers at 70 eV. Elemental analysis was carried out using a CE440 Elemental Analyser purchased from Exeter Analytical (UK) Ltd. Optical rotations were measured on a Perkin- Elmer 241 polarimeter.

Materials

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Flash chromatography was carried out using silica gel 60 (0.040-0.063mm, 230-400 mesh) as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with silica gel 60, which were visualized by quenching of u.v. fluorescence (λ_{max} = 254 nm) or by staining with either 10% w/v ammonium molybdate in 2 M sulfuric acid or basic potassium permanganate solution (followed by heat) as appropriate.

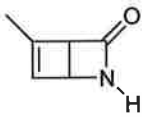
4.1 Experimental Details for Chapter 4.

2-aza-bicyclo[2.2.0]hex-5-en-3-one (4.2a).



1*H*-Pyridin-2-one **4.1a** (0.02 mol) in CH_3CN (500 mL) was irradiated with UV light (300 nm) at room temperature for 72h using a Hanovia reactor. The crude product was purified by neutral Al_2O_3 column chromatography (eluent: petroleum ether / ethyl acetate 1 : 1) to give compound **4.2a** as a pale yellow solid (50% yield). mp= 293 K, R_f = 0.10 (eluent: petroleum ether / ethyl acetate 1 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 6.59 (1H, m), 7.98 (1H, m), 4.38 (1H, m), 4.11 (1H, m); ^{13}C-NMR (106.6 MHz) δ_C 172.1, 142.5, 140.5, 59.6, 50.8; HRMS found: M^+ 95.0375, C_5H_5NO requires 95.0371, *m/z*: 95 (100%, M^+).

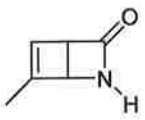
5-methyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one (4.2c).



4-Methyl-pyridone **4.1c** (0.5 mmol) in ethyl acetate (500 mL) was irradiated with UV light (300 nm) for 2h at room temperature. The crude product was purified by neutral Al_2O_3 column chromatography (eluent: petroleum ether ethyl acetate 1 : 1) to give compound **4.2c** as a colourless solid (75% yield), mp= 315 K, R_f = 0.15 (eluent: petroleum ether / ethyl acetate 1 : 1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 6.12 (1H, m), 4.21 (1H, m), 3.99 (1H, m), 1.85 (3H, m); ^{13}C-NMR (106.6 MHz, $CDCl_3$) δ_C 172.8, 151.7, 134.4, 61.0, 47.2, 16.5.

6-methyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one (4.2d).



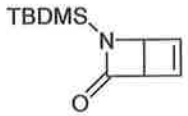
5-Methyl-pyridone **4.1c** (0.5 mmol) in ethanol (500 mL) was irradiated with UV light (300 nm) for 20h at room temperature. The crude product was purified by neutral Al_2O_3 column chromatography (eluent: petroleum ether ethyl acetate 1 : 1) to give compound **4.2d** as a colourless solid (70% yield), mp= 319 K, R_f = 0.16(eluent: petroleum ether / ethyl acetate 1 : 1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 6.16 (1H, m), 4.18 (1H, m), 3.96 (1H, m), 1.87 (3H, m); ^{13}C-NMR (106.6 MHz, $CDCl_3$) δ_C 172.3, 152.1, 134.2, 61.8, 46.2, 16.1.

Procedure for the preparation of compounds 4.18 and 4.20.

To a solution of compound **4.2a** (1mmol) in DMF (2 mL) at r.t. were sequentially added imidazole (1.1 mmol) and tert-butyldimethylsilyl chloride (1.3 equiv). The reaction was stirred for 2 h, then extracted with diethyl ether (3 x 10 mL). The combined organic layer was washed with saturated NaCl (10 mL), then dried over Na_2SO_4 and evaporated in vacuo. The crude residue was purified by silica gel column chromatography (previously deactivated with NEt_3) (eluent: diethyl ether / petroleum ether 1 : 5) to give compounds **4.18-4.20.**

2-(tert-Butyl-dimethylsilanyl)2-aza-bicyclo[2.2.0]hex-5-en-3-one (4.20).



Yellow oil, yield: 63%, Rf = 0.68 (eluent: diethyl ether / petroleum ether 1 : 5).

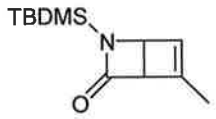
^{1}H-NMR (400 MHz, $CDCl_3$) δH 6.60 (1H, m), 6.49 (1H, m), 4.31 (1H, m), 4.14 (1H, m), 0.92 (9H, s), 0.20 (3H, s), 0.17 (3H, s); ^{13}C-NMR (100.6 MHz) δ_C 175.3, 143.0, 141.2, 60.1,

52.0, 25.9, 18.2, -6.3, -6.7; HRMS found: M+ 209.1237, $C_{11}H_{19}NOSi$ requires 209.1236, m/z: 209 (100%, M^+).

Procedure for the preparation of compounds 4.21 and 4.23.

To a solution of compound **4.2a** or **4.2c** (1 mmol) in DMF (2 mL) at 0 °C were sequentially added triethylamine (1.3 mmol) and tert-butyldimethylsilyl chloride (1.3 equiv). The reaction was allowed to reach room temperature and stirred for 2 h, then extracted with diethyl ether (3 x 10 mL). The combined organic layer was washed with saturated NaCl (10 mL), then dried over Na_2SO_4 and evaporated in vacuo. The crude residue was purified by silica gel column chromatography (previously deactivated with NEt_3) (eluent: diethyl ether / petroleum ether 1 : 5) to give compounds **4.21** and **4.23**.

2-(tert-Butyl-dimethylsilanyl)-5-methyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one (4.23).



Yellow oil, yield: 90%, Rf = 0.63 (eluent: diethyl ether / petroleum ether 1 : 5).

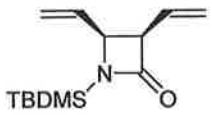
^{1}H-NMR (400 MHz, $CDCl_3$) δH 6.15 (1H, m), 4.15 (1H, m), 4.03 (1H, m), 1.89 (3H, m), 0.92 (9H,s), 0.20 (3H,s), 0.16 (3H, s); ^{13}C-NMR (106.6 MHz, $CDCl_3$) δ_C 175.8, 152.3, 134.9, 61.5, 48.3, 25.9, 18.2, 16.7, -6.3, -6.7; HRMS found: M+ 223.1402, $C_{12}H_{21}NOSi$ requires 223.1392, m/z: 223 (100%, M^+).

Procedure for the preparation of compounds 4.26 and 4.29.

To a solution of compound **4.20** or **4.23** (1 mmol) in dry CH_2Cl_2 (7 mL), were added Grubbs' cat. I generation catalyst (10% mol) dissolved in dry CH_2Cl_2 (7mL) and ethylene under pressure (300 psi). After 4 h the reaction was filtered, the organic layer evaporated *in vacuo*

and the crude residue purified by silica gel column chromatography (eluent: diethyl ether / petroleum ether 1 : 5) to give compound **4.26** or **4.29**. It was important to deactivate the silica gel using NEt_3 prior to use.

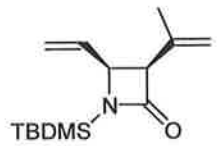
1-(*tert*-Butyl-dimethylsilanyl)-3,4-divinyl-azetidin-2-one (4.26).



Yellow oil, yield 85%, R_f = 0.85 (eluent: diethyl ether / petroleum ether 1 : 1).

IR: ν_{max} (neat) / cm^{-1}: 3241, 2932, 1765; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.81-5.66 (2H, m), 5.33-5.19 (4H, m), 4.15-4.04 (2H, m), 0.93 (9H, s), 0.20 (3 H, s), 0.16 (3 H, s); ^{13}C-NMR (106.6 MHz, $CDCl_3$) δ_C 173.1, 137.3, 129.6, 119.7, 119.1, 59.0, 56.8, 26.4, 18.4,-5.3,-5.5; HRMS found: M^+ 237.1555, $C_{13}H_{23}NOSi$ requires 237.1549, *m/z*: 237(100%, M^+).

1-(*tert*-Butyl-dimethylsilanyl)-3-isopropenyl-4-vinyl-azetidin-2-one (4.29).



Dark oil, yield 90%, Rf = 0.83 (eluent diethyl ether / petroleum ether 1 : 1).

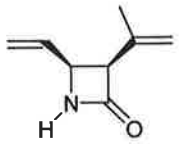
IR: vmax (neat) / cm^{-1}: 3080, 1758, 1415, 891; ^{1}H-NMR (400 MHz, $CDCl_3$) δH 5.69 (1H, dt, *J* = 17.2, 10.0 Hz), 5.20 (1H, dd, *J* = 17.2, 1.4 Hz), 5.12 (1H, dd, *J* = 10, 1.4 Hz), 4.99 (1H, s), 4.89 (1H, s), 4.01 (1H, dd, *J* = 10, 6 Hz), 3.93 (1H, d, *J* = 6 Hz), 1.51 (3H, s), 0.85 (9H, s), 0.10 (3H, s), 0.09 (3H, s); ^{13}C-NMR (106.6 MHz, $CDCl_3$) δC 173.0; 137.39; 136.82;

119.3; 114.5; 61.6; 56.6; 26.3; 22.2; 18.3; -5.2; -5.59; HRMS found: M^+ 251.1704, $C_{14}H_{25}NOSi$ requires 251.1705, m/z: 251 (100%, M^+).

Procedure for the preparation of compounds 4.30.

To a solution of *N*-TBDMS protected azetidinone **4.29** (1 mmol) in methanol (10 mL) at -20°C was slowly added solid potassium fluoride (1.1 mmol). The reaction mixture was stirred for 50 min, and the solvent was evaporated in vacuo. The crude was purified by flash column chromatography (eluent: petroleum ether / ethyl acetate 1 : 1) to afford compound **4.30**.

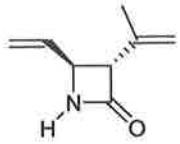
***Cis* 3-isopropenyl-4-vinyl-azetidin-2-one (*cis*-4.30).**



Brown oil, yield 75%, R_f = 0.53 (eluent: petroleum ether / ethyl acetate 1 : 1).

IR: ν_{max} (neat) / cm^{-1}: 3235, 2927, 1755; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.75 (1H, ddd, *J* = 17.2, 10.0, 7.6 Hz), 5.26 (1H, d, *J* = 17.2 Hz) 5.20 (1H, d, *J* = 10.0 Hz), 5.01 (1H, s), 4.96 (1H, s), 4.21-4.18 (1H, m), 3.91 (1H, d, *J* = 5.6 Hz), 1.59 (3H, s); ^{13}C-NMR (100.6 MHz) δ_C 168.4, 138.1, 136.9, 119.2; 115.1, 61.5, 54.5, 22.2; HRMS found: M^+ 137.0846, $C_8H_{11}NO$ requires 137.0841, *m/z*: 137 (100%, M^+).

***Trans* 3-isopropenyl-4-vinyl-azetidin-2-one (*trans*-4.30):**

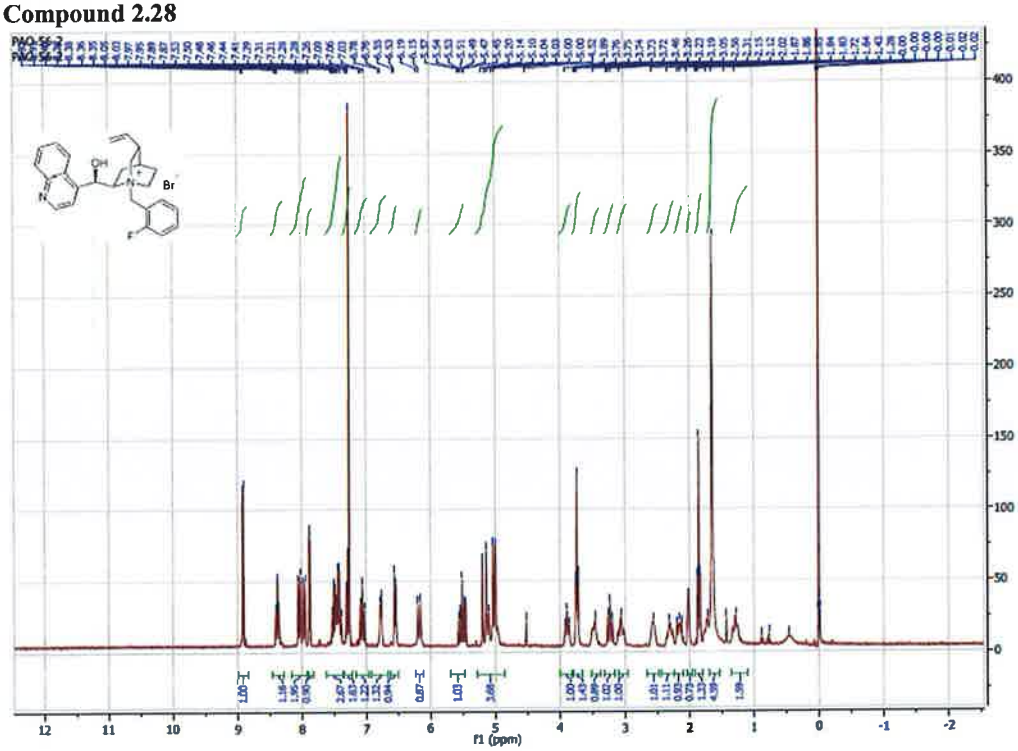


Brown oil, yield 8%, R_f = 0.47, (petroleum ether : ethyl acetate 1 : 1).

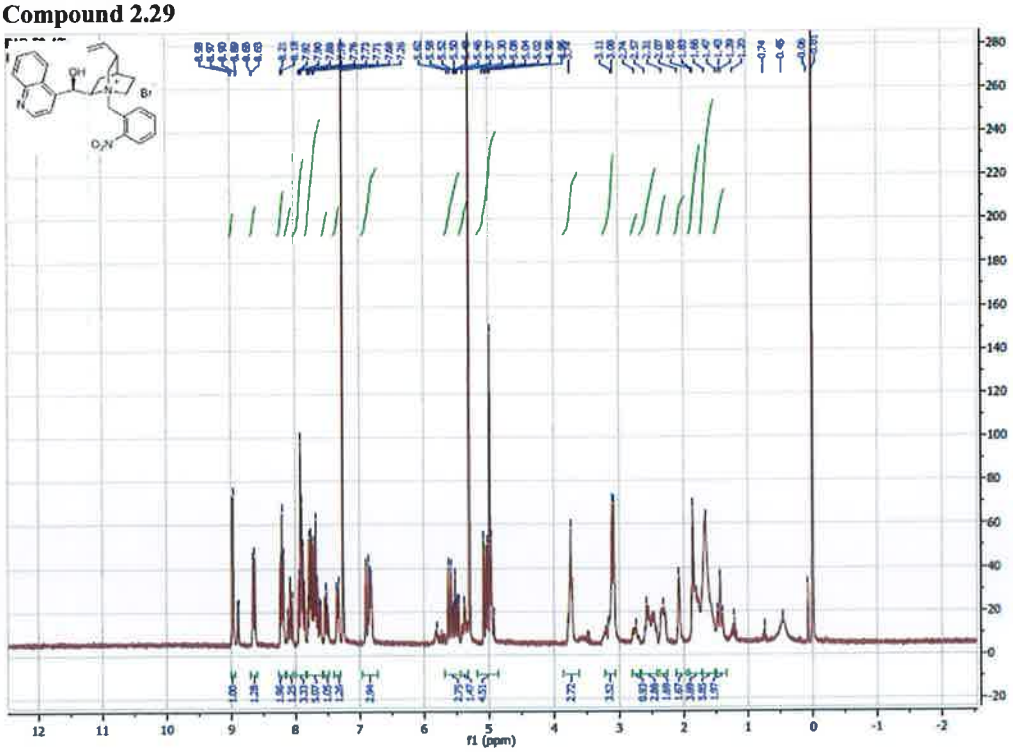
IR: ν_{max} (neat) / cm^{-1}: 3232, 2928, 1754; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.97 (1H, ddd, J = 17.2, 10.4, 7.2 Hz), 5.34 (1H, d, J = 17.2 Hz), 5.22 (1H, d, J = 10.4 Hz), 5.00 (1H, apps) 4.96 (1H, apps), 4.00 (1H, dd, J = 7.2, 2 Hz), 3.52 (1 H, m, J = 2 Hz), 1.82 (3H, s); ^{13}C-NMR (100.6 MHz) δ_C 168.2, 138.1, 137.0, 117.4; 114.1, 65.2, 55.7, 29.7; HRMS found: M^+ 137.0846, $C_8H_{11}NO$ requires 137.0841, *m/z*: 137 (100%, M^+).

Copies of the ^{1}H NMR, ^{13}C NMR and HPLC spectra for Chapter 2.

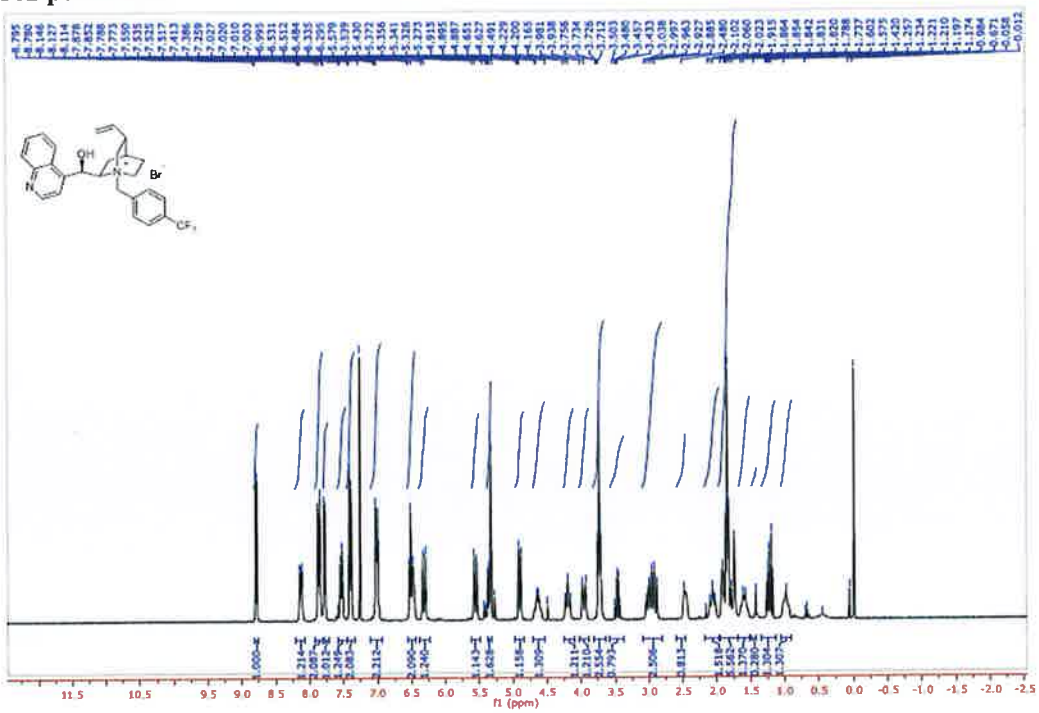
Compound 2.28



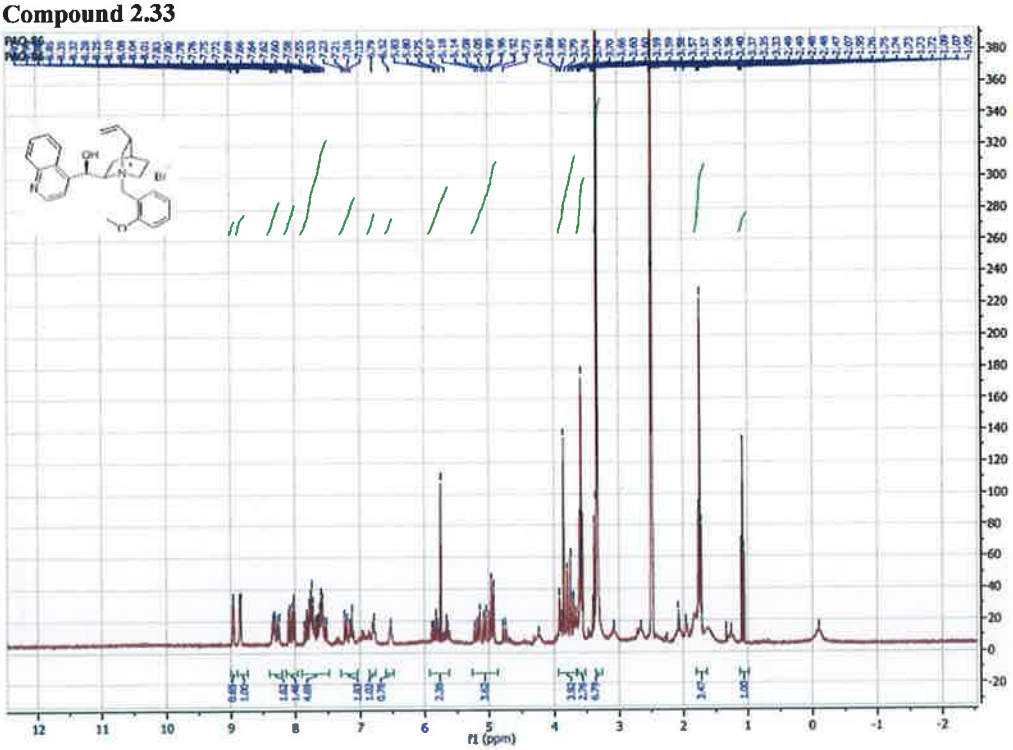
Compound 2.29



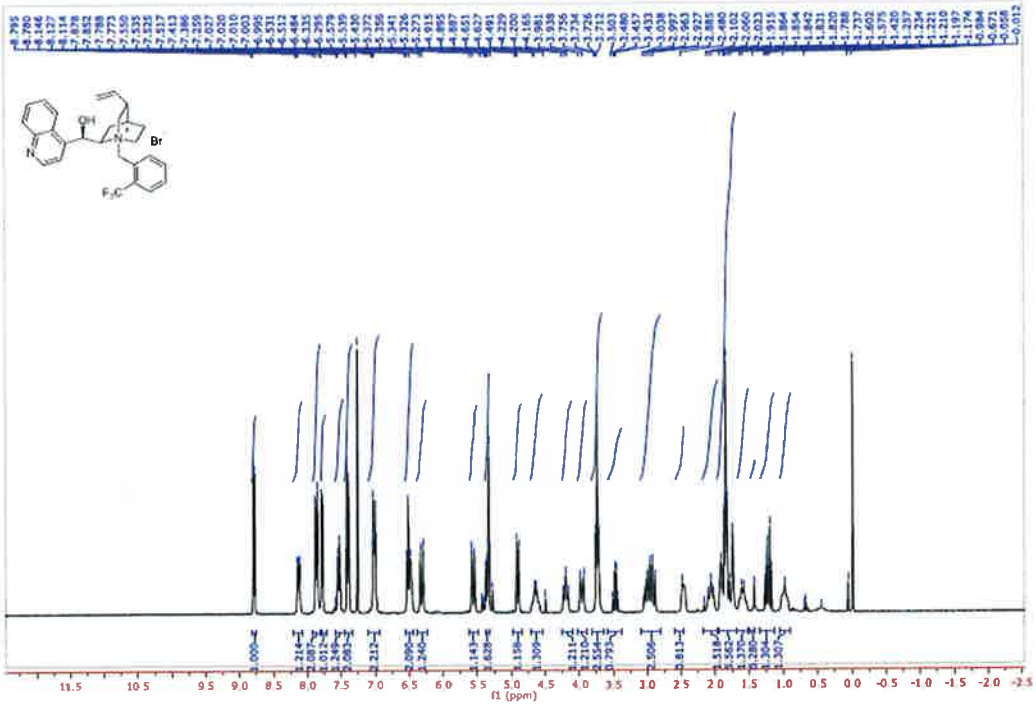
Compound 2.31



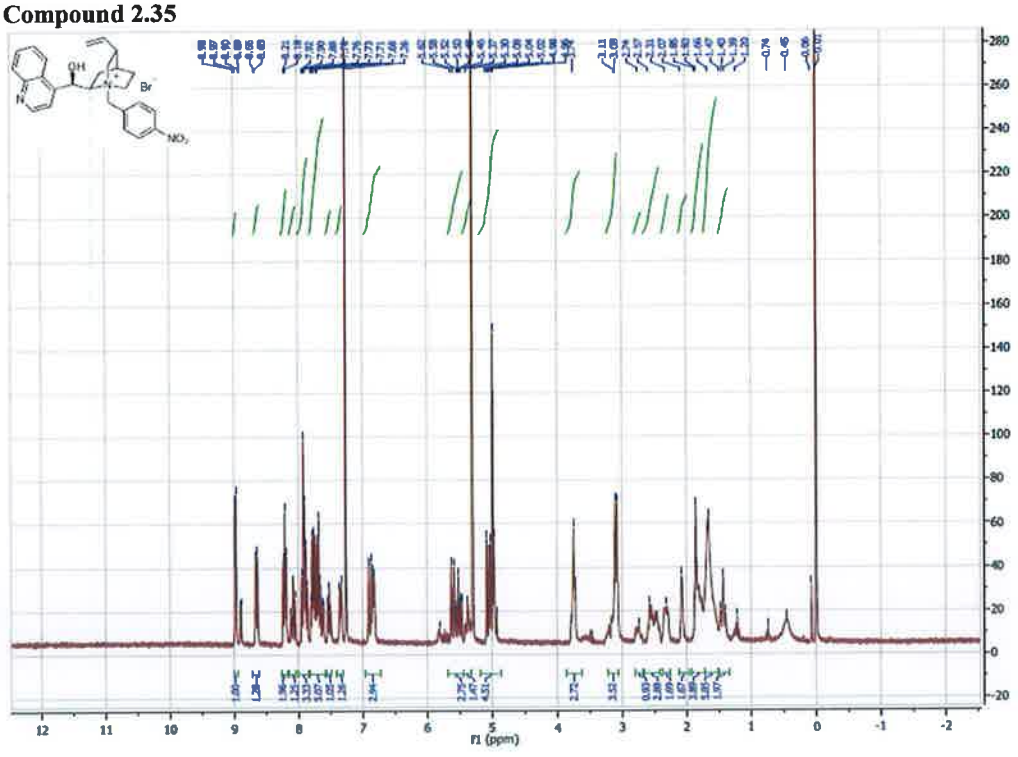
Compound 2.33



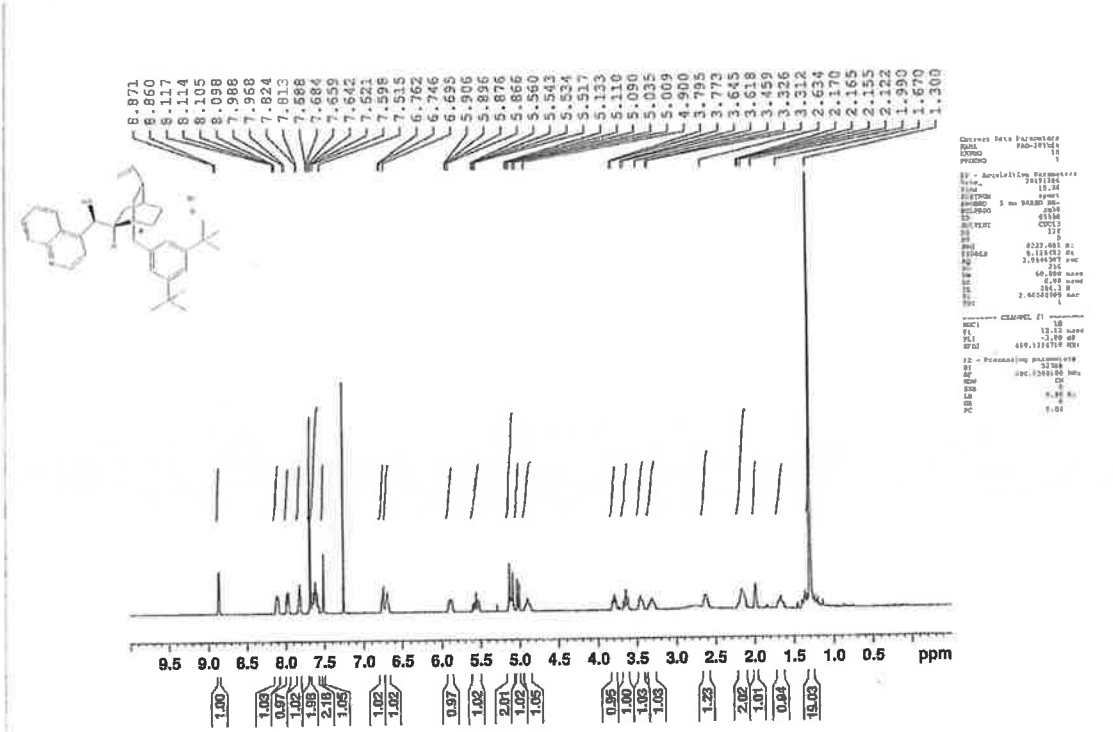
Compound 2.34

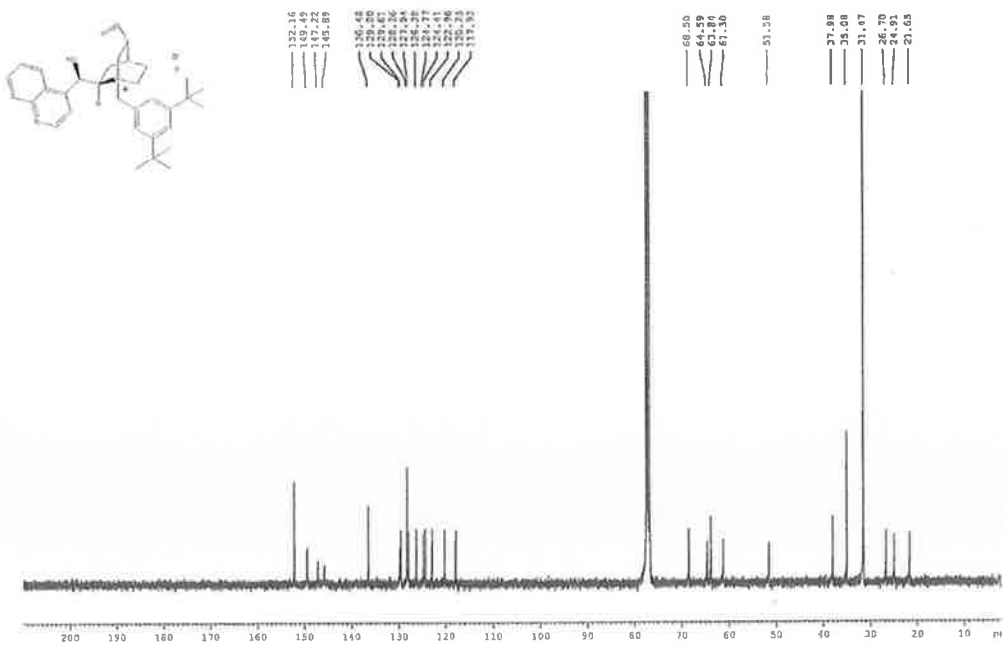


Compound 2.35

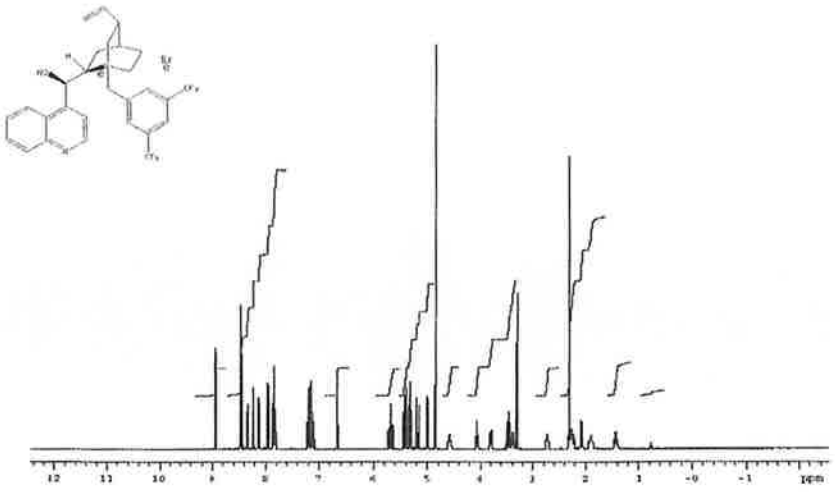


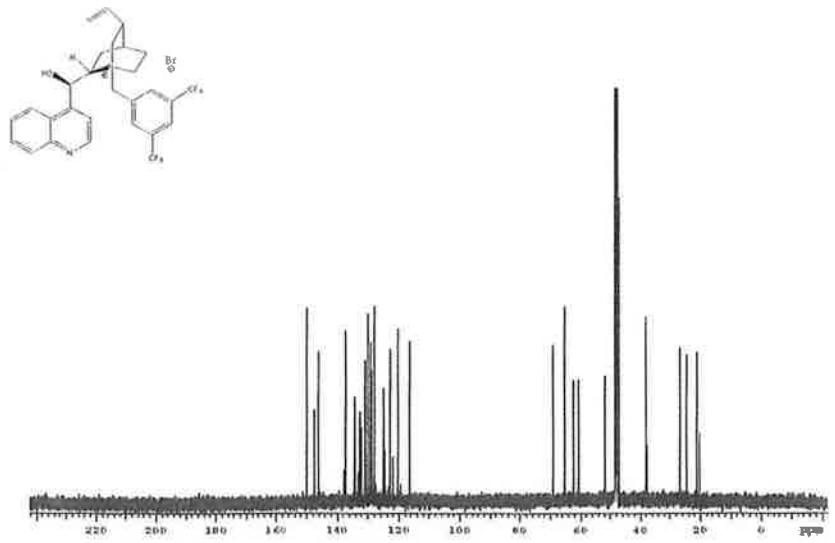
Compound 2.38

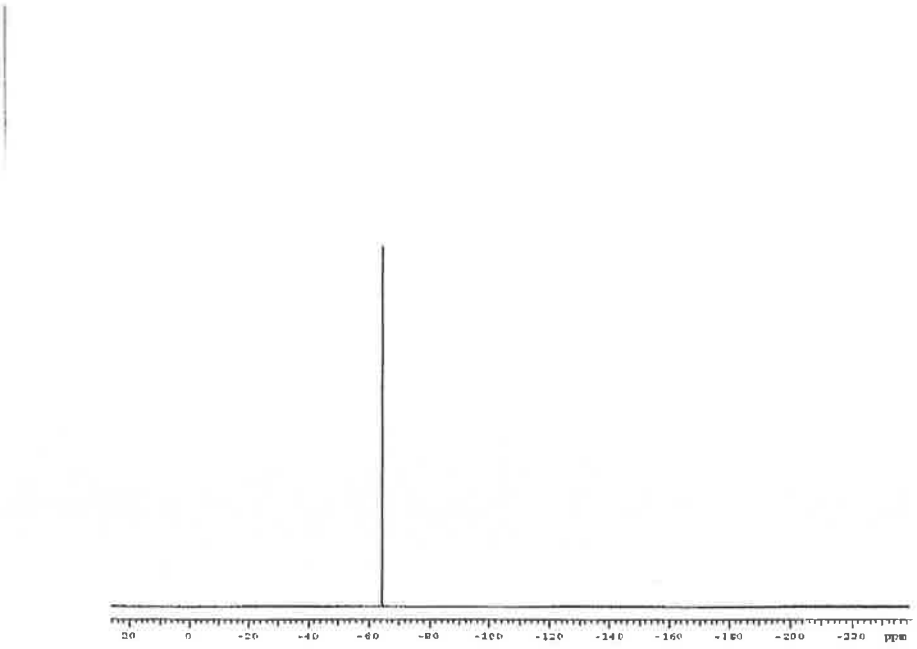




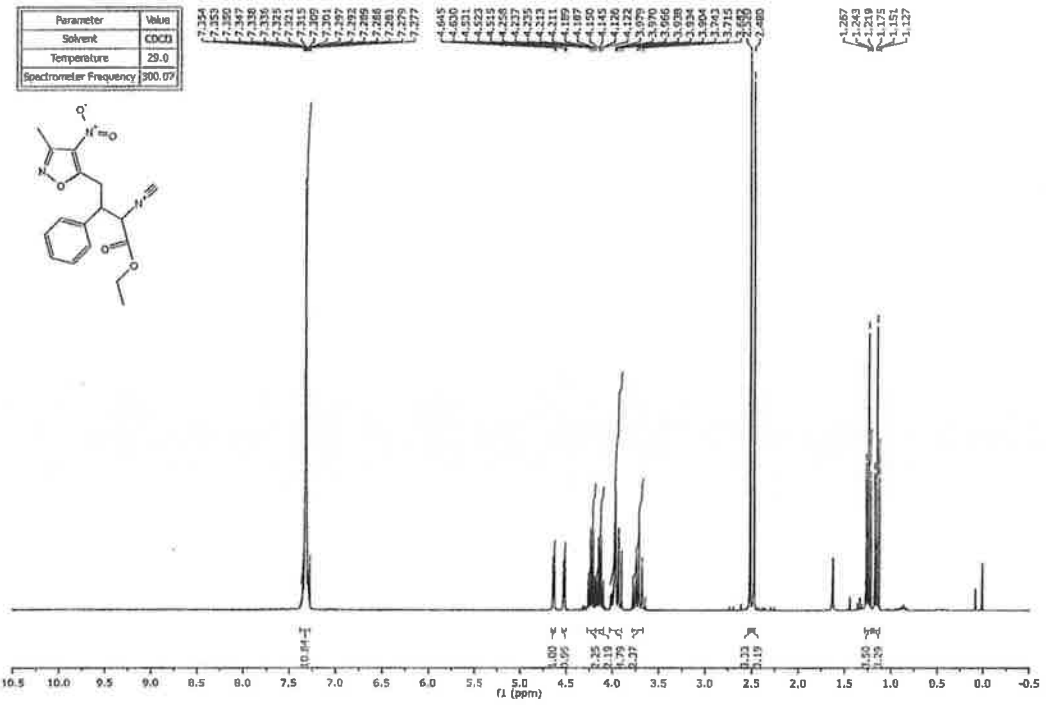
Compound 2.39

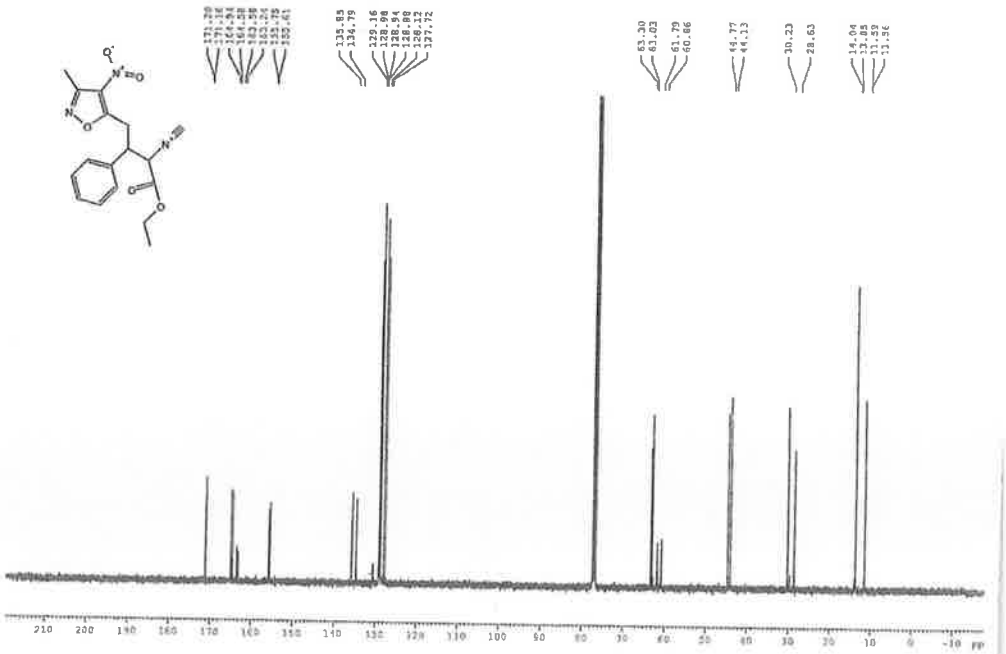




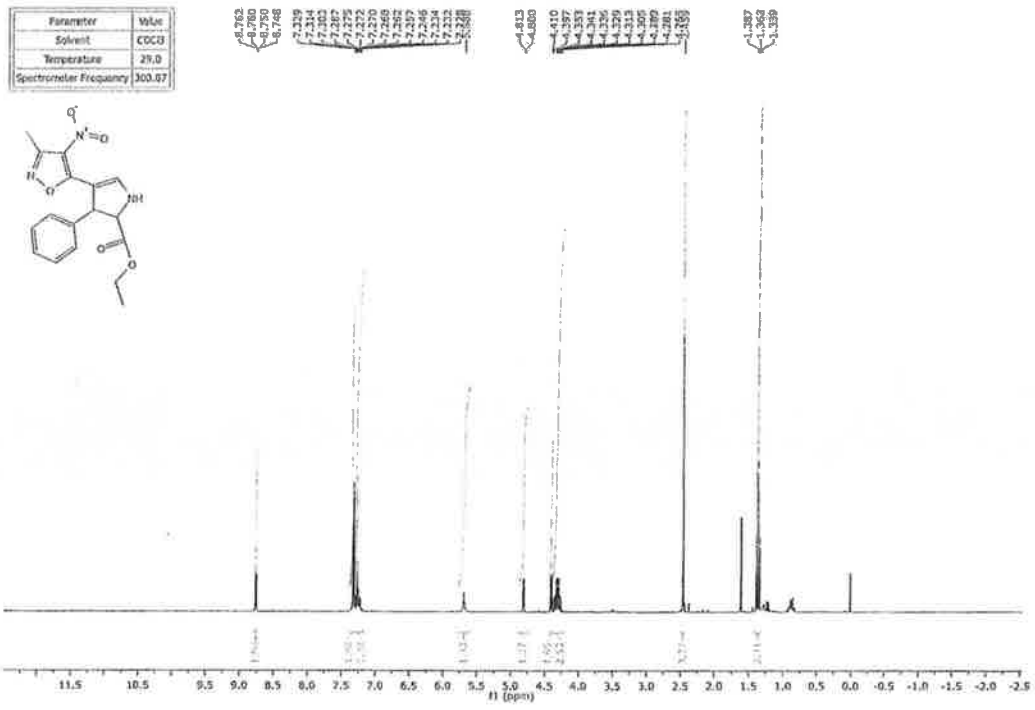

20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

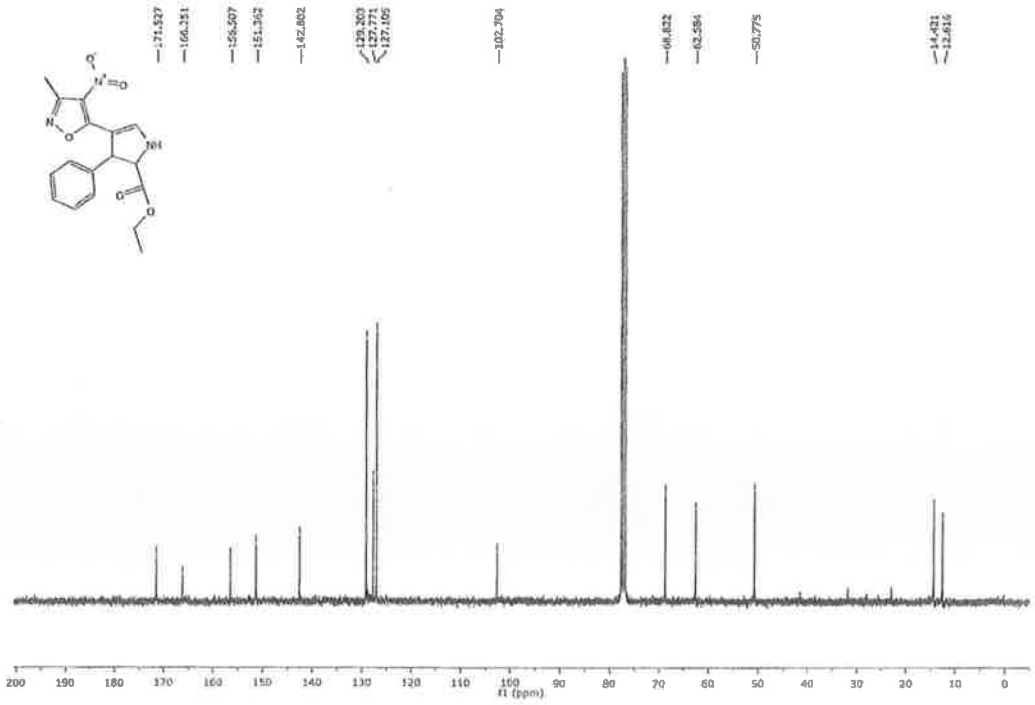
Compound 2.19a





Compound 2.20a

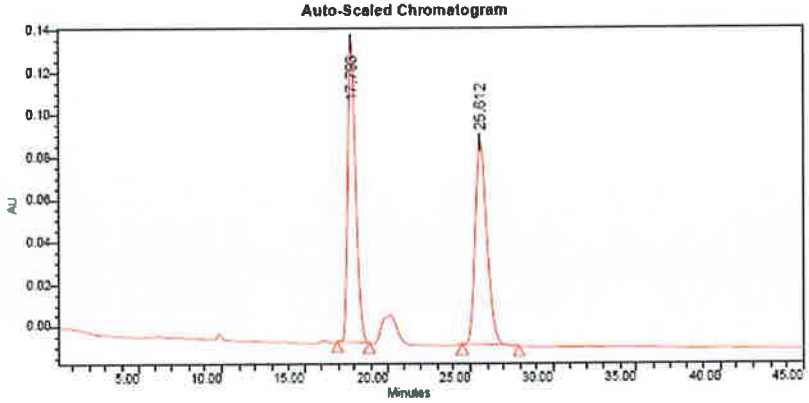




SAMPLE INFORMATION

Sample Name:	PAO-racemo	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	6/23/10 12:07:48 PM
Vial:	1	Acq. Method Set:	Chiralmiscela
Injection #:	1	Date Processed:	6/23/10 1:19:02 PM
Injection Volume:	10.00 ul	Processing Method:	HPLC
Run Time:	45.0 Minutes	Channel Name:	PDA Single 254.0 nm
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm

Auto-Scaled Chromatogram



Unknown Peak Results

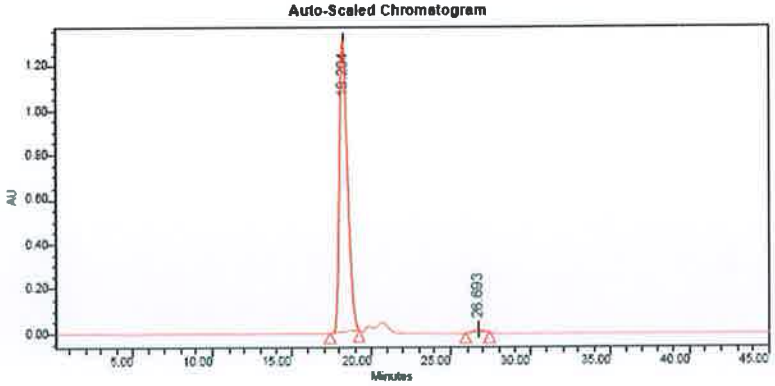
	Peak Type	RT	Area	% Area	Height
1	Unknown	17.793	4762780	50.19	141051
2	Unknown	25.612	4716972	49.81	95737

Compound 2.20a

SAMPLE INFORMATION

Sample Name:	PAO-234	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	6/22/10 4:25:36 PM
Vial:	1	Acq. Method Set:	Chiralmiscela
Injection #:	2	Date Processed:	7/1/10 10:43:30 AM
Injection Volume:	10.00 ul	Processing Method:	HPLC
Run Time:	45.0 Minutes	Channel Name:	PDA Single 421.0 nm
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm

Auto-Scaled Chromatogram



Unknown Peak Results

	Peak Type	RT	Area	% Area	Height
1	Unknown	18.204	46652143	98.45	1302651
2	Unknown	26.693	735631	1.55	16491

Compound *ent*-2.20a

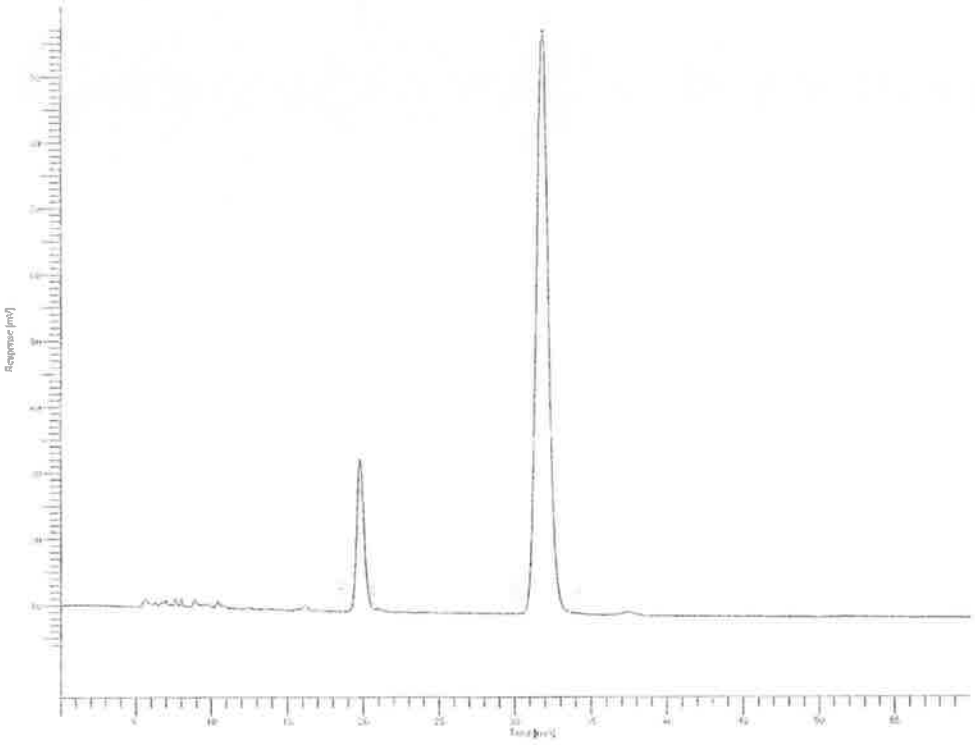
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		19.763	746200.13	22607.13	13.35	13.35			*MM	0.7462	0.7462
2		31.797	4844007.15	88362.66	86.65	86.65			*MM	4.8440	4.8440
			5590207.28	110969.79	100.00	100.00				5.5902	5.5902

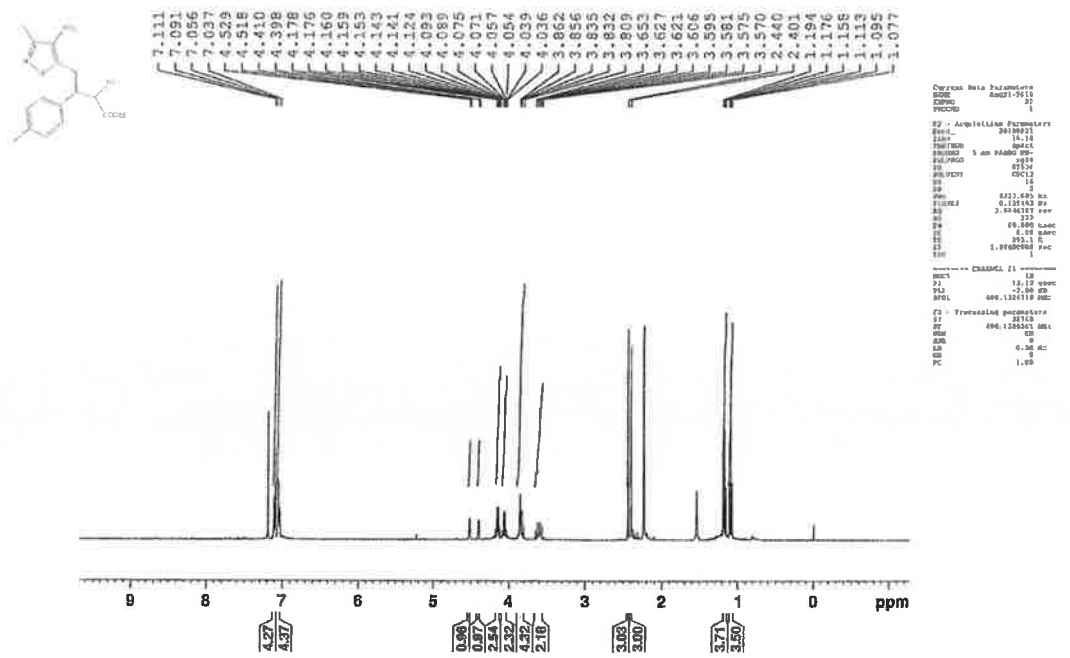
Missing Component Report

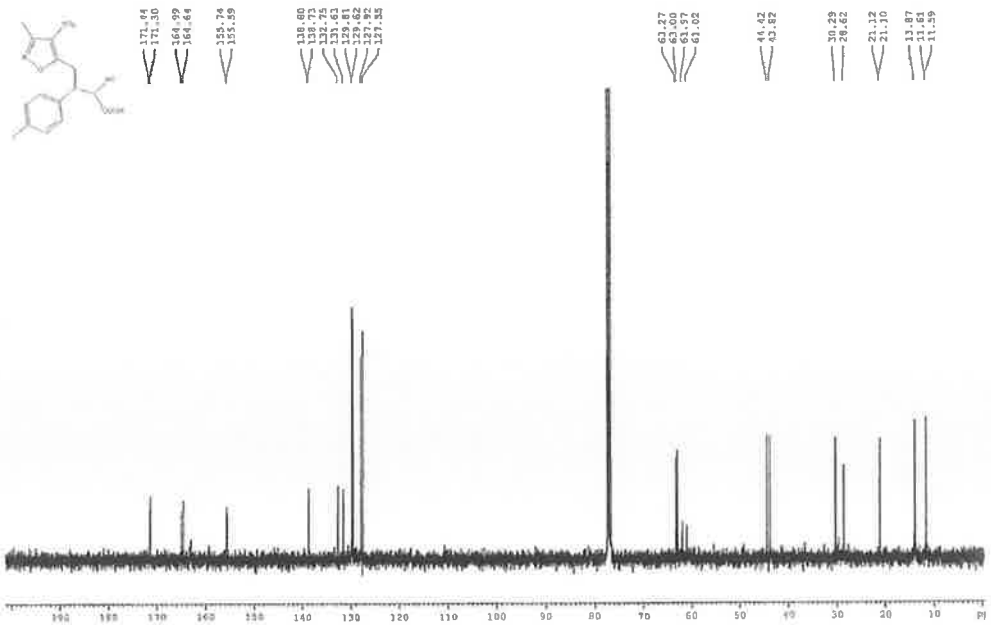
Component	Expected Retention (Calibration File)

All components were found

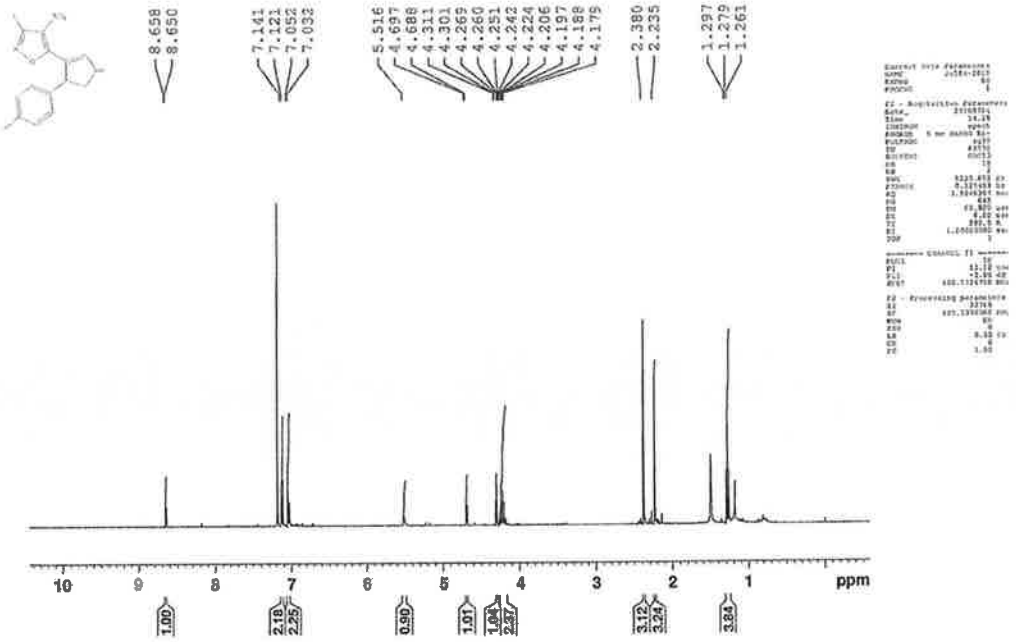


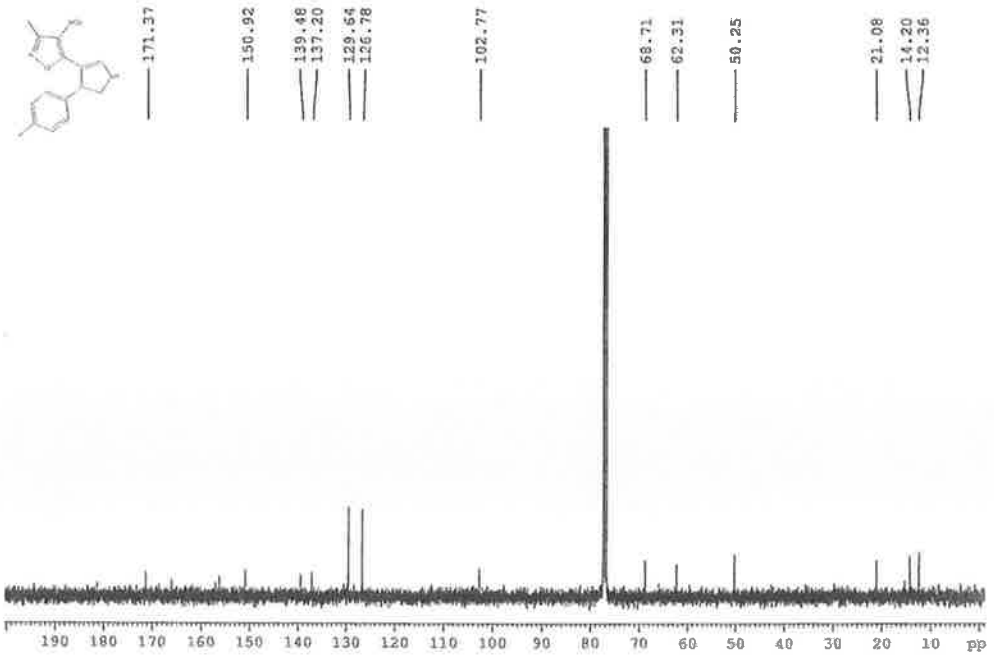
Compound 2.19b





Compound 2.20b





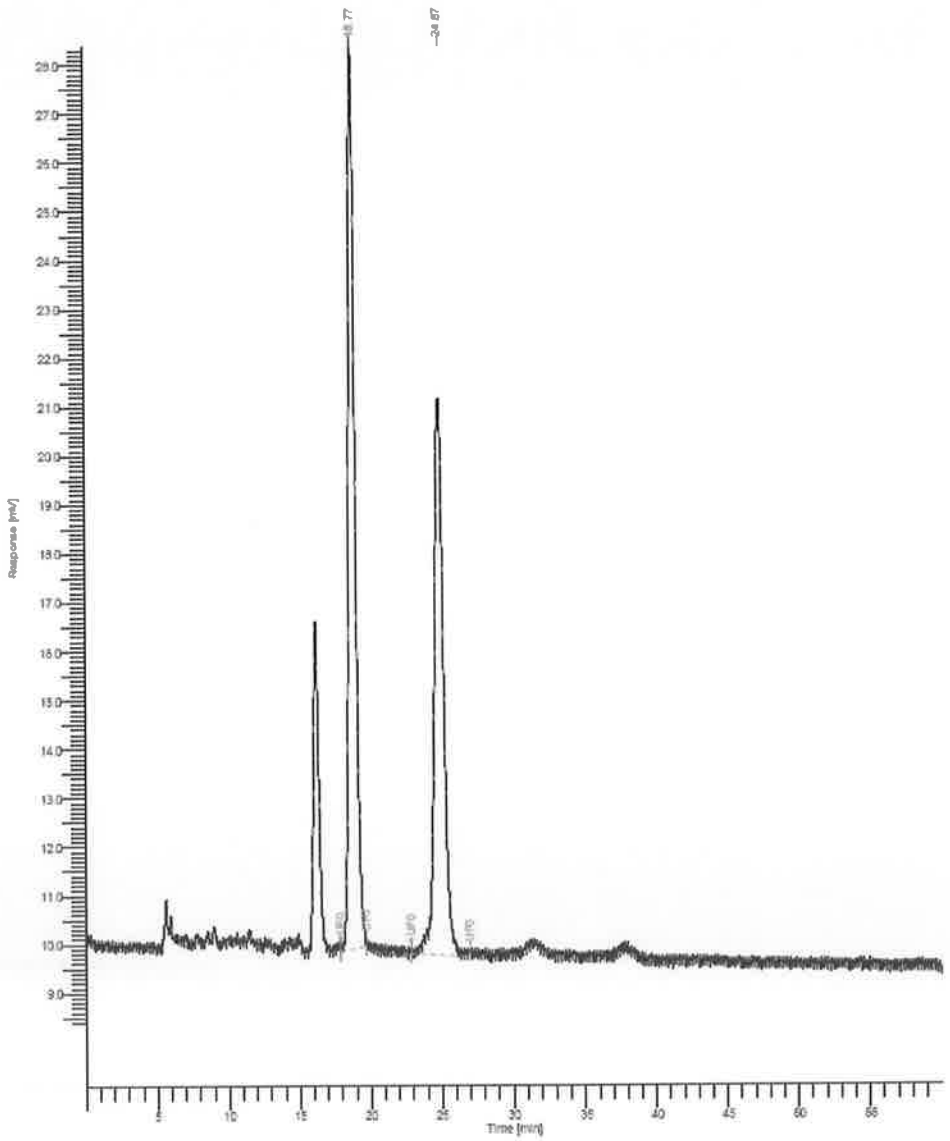
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.773	596529.70	18485.47	53.95	53.95			*MM	0.5965	0.5965
2		24.875	509132.54	11395.26	46.05	46.05			*MM	0.5091	0.5091
			1105662.24	29880.73	100.00	100.00				1.1057	1.1057

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20b

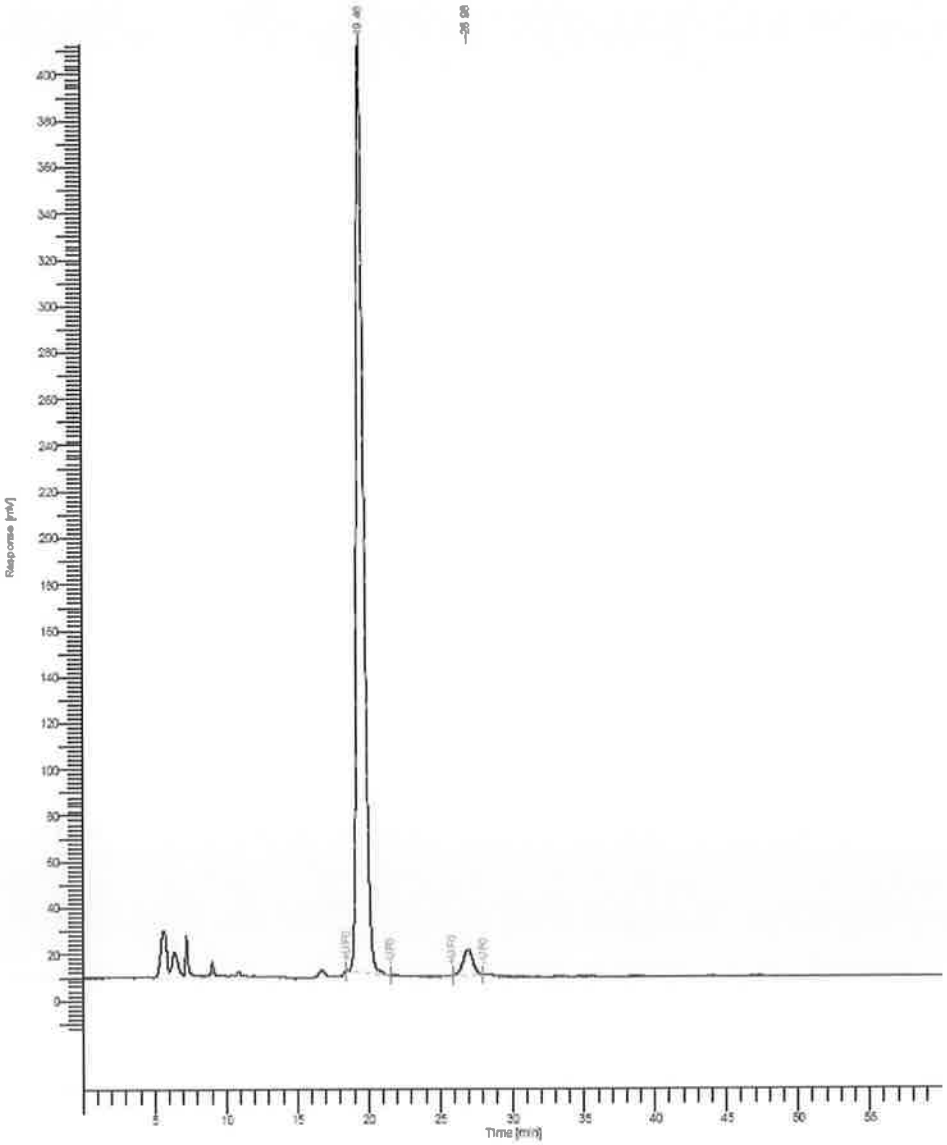
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		19.463	14140770.84	400803.08	96.34	96.34			*MM	14.1408	14.1408
2		26.979	536476.70	11150.75	3.66	3.66			*MM	0.5365	0.5365
			14677247.54	411953.83	100.00	100.00				14.6772	14.6772

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound *ent*-2.20b

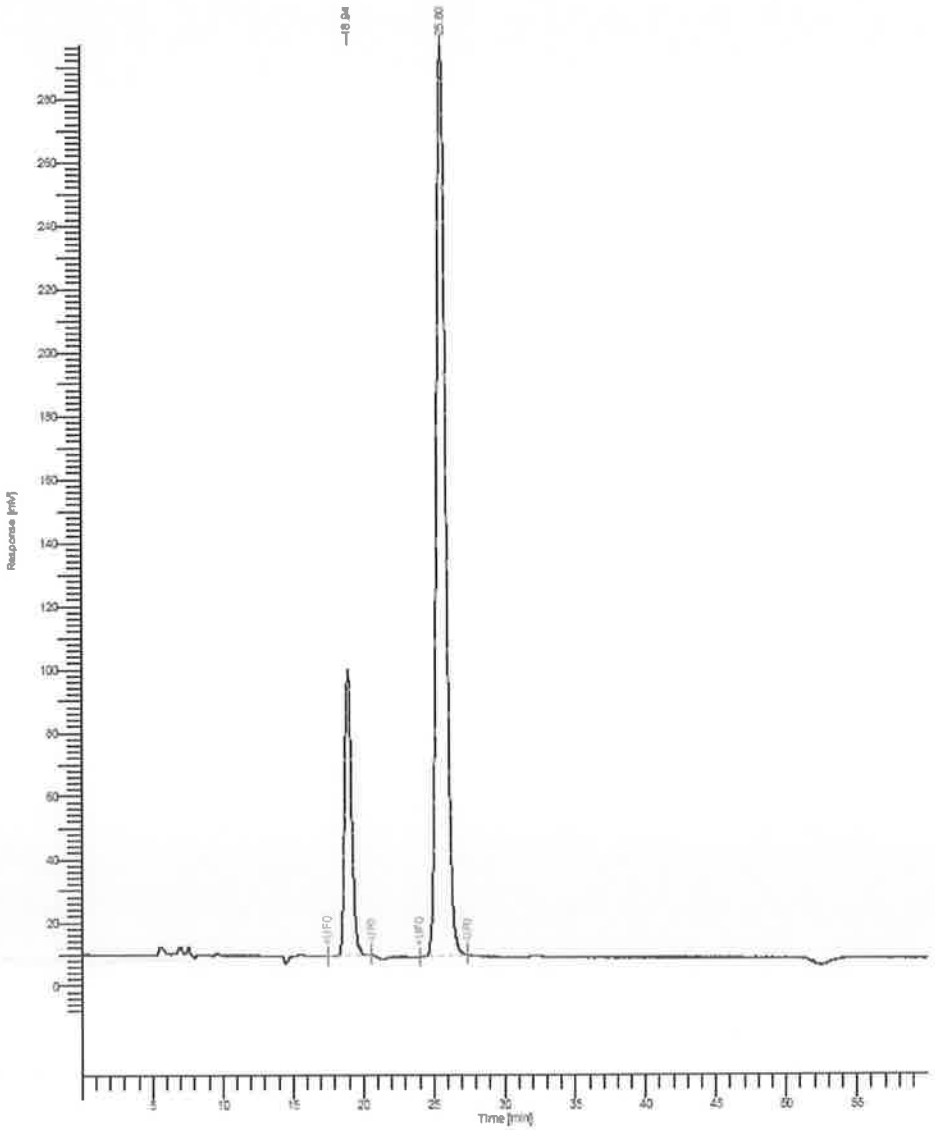
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.942	2988890.68	90490.68	18.70	18.70			*MM	2.9889	2.9889
2		25.601	12993463.36	287572.21	81.30	81.30			*MM	12.9935	12.9935
			15982353.94	378062.88	100.00	100.00				15.9824	15.9824

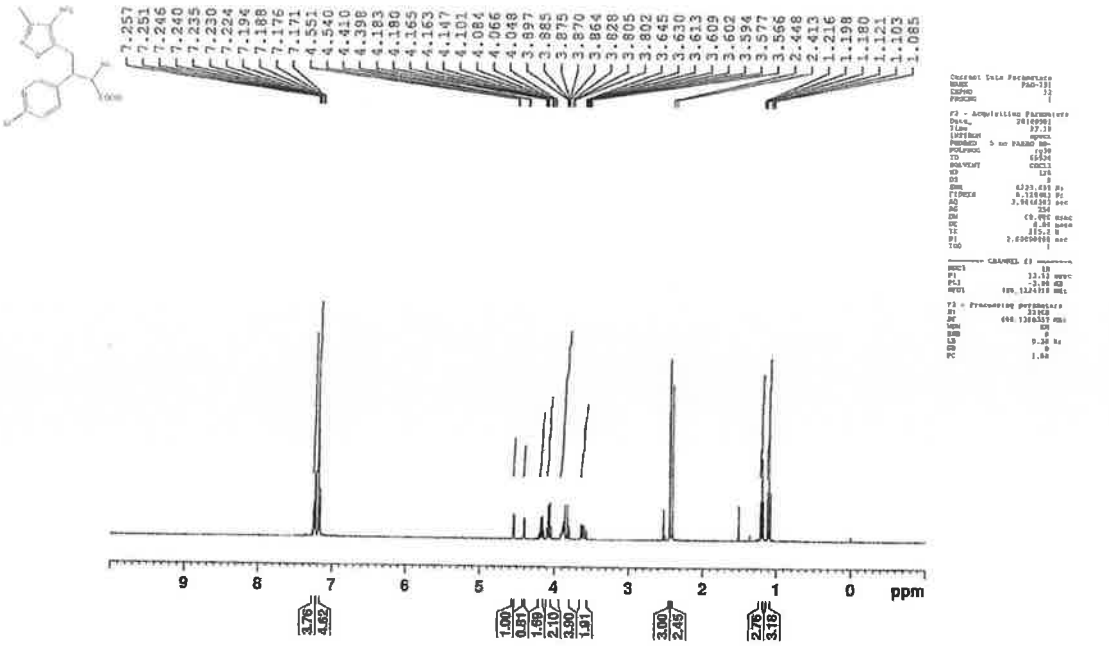
Missing Component Report

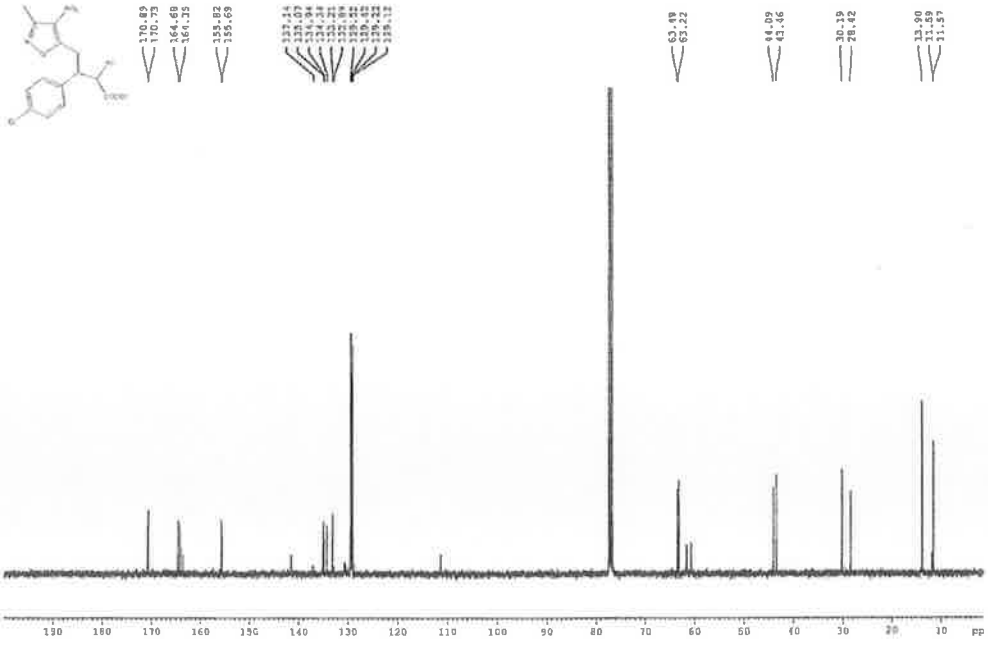
Component	Expected Retention (Calibration File)

All components were found



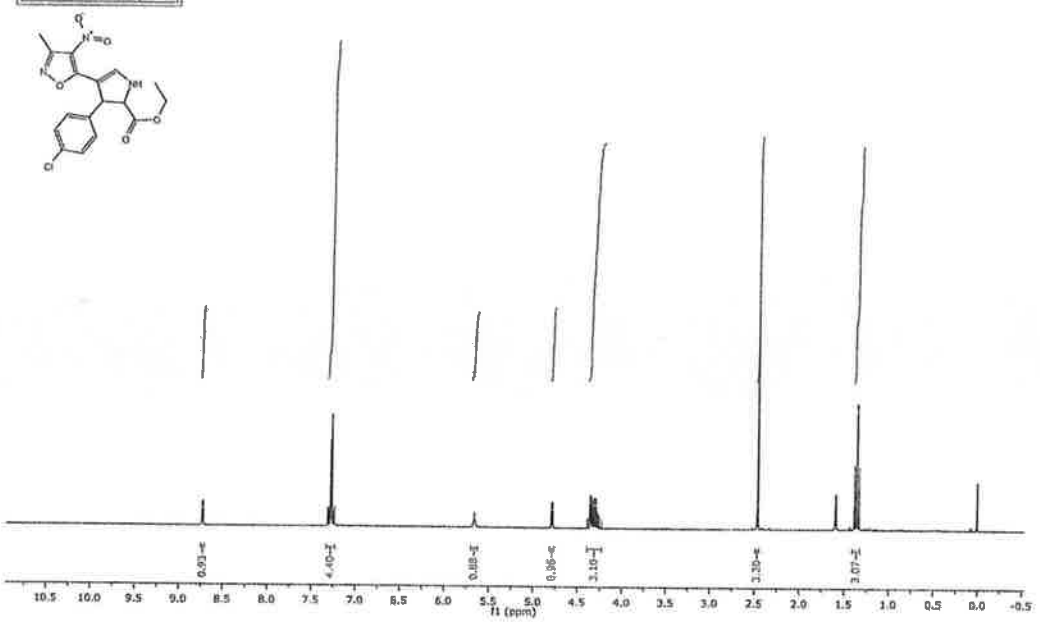
Compound 2.19c

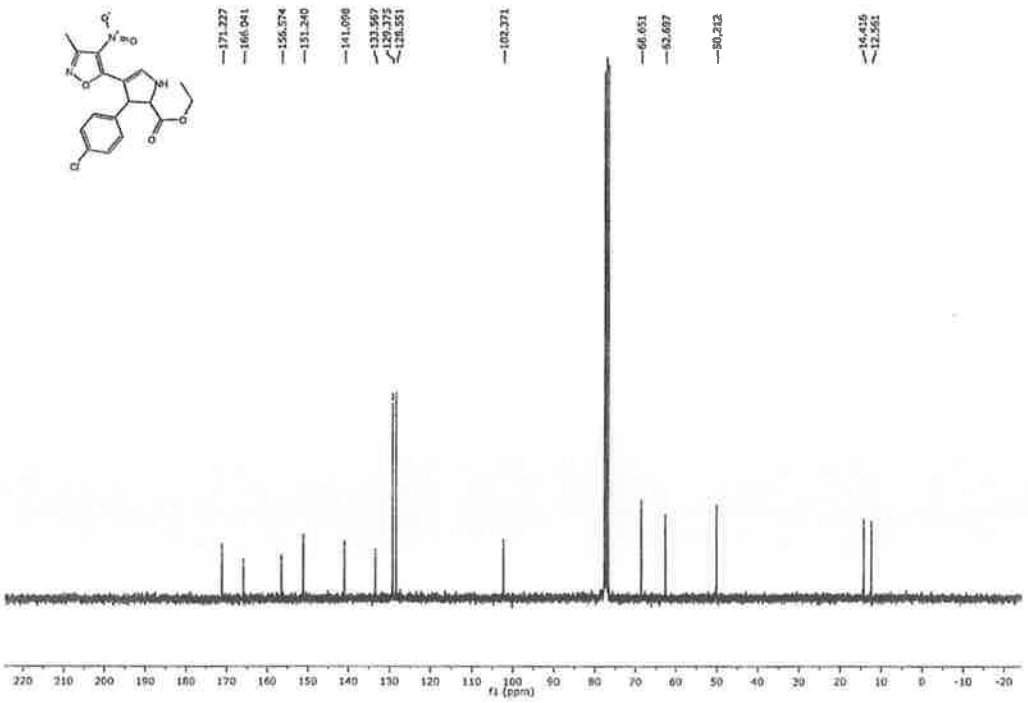




Compound 2.20c

Parameter	Value
Solvent	CDCl3
Temperature	29.0
Spectrometer Frequency	300.07





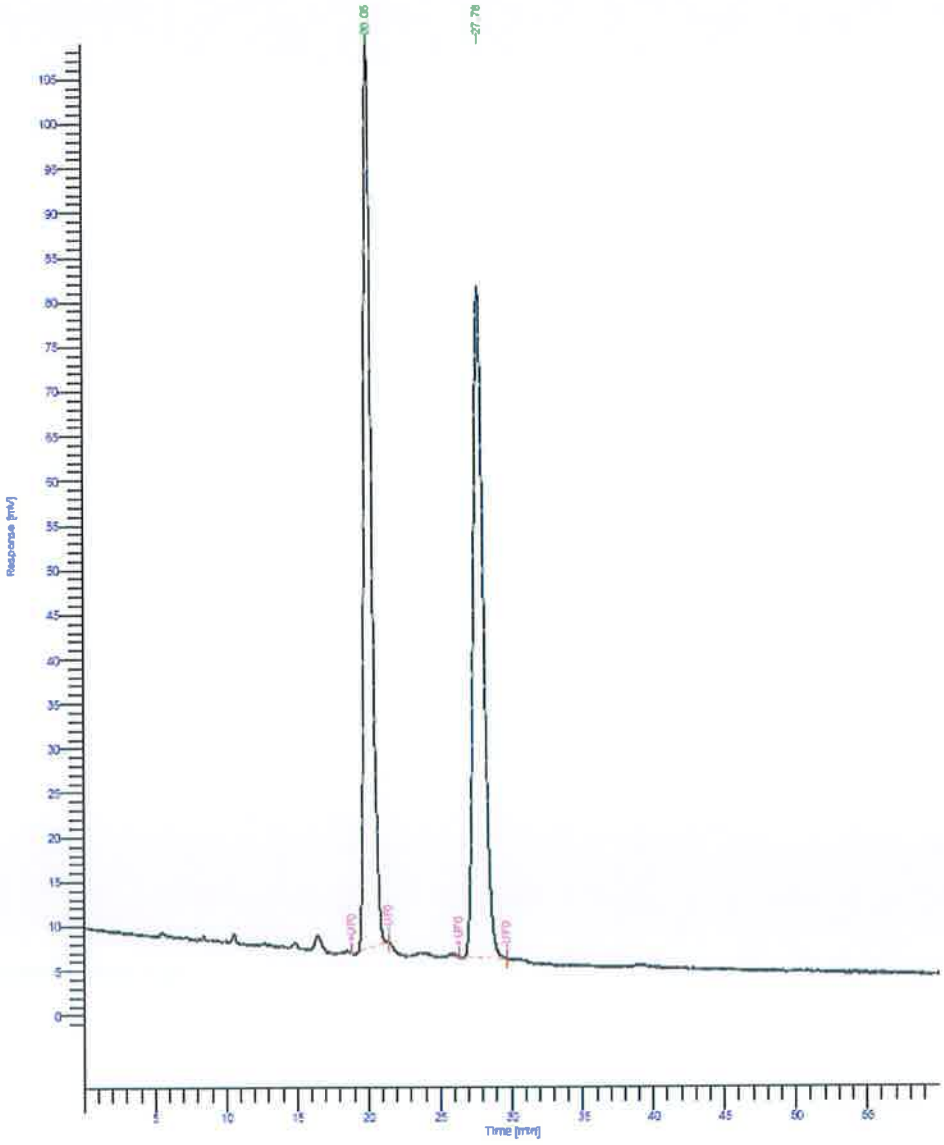
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		20.049	3719948.02	101367.32	49.79	49.79			"MM	3.7199	3.7199
2		27.779	3750705.39	75261.17	50.21	50.21			"MM	3.7507	3.7507
			7470653.41	176628.49	100.00	100.00				7.4707	7.4707

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20c

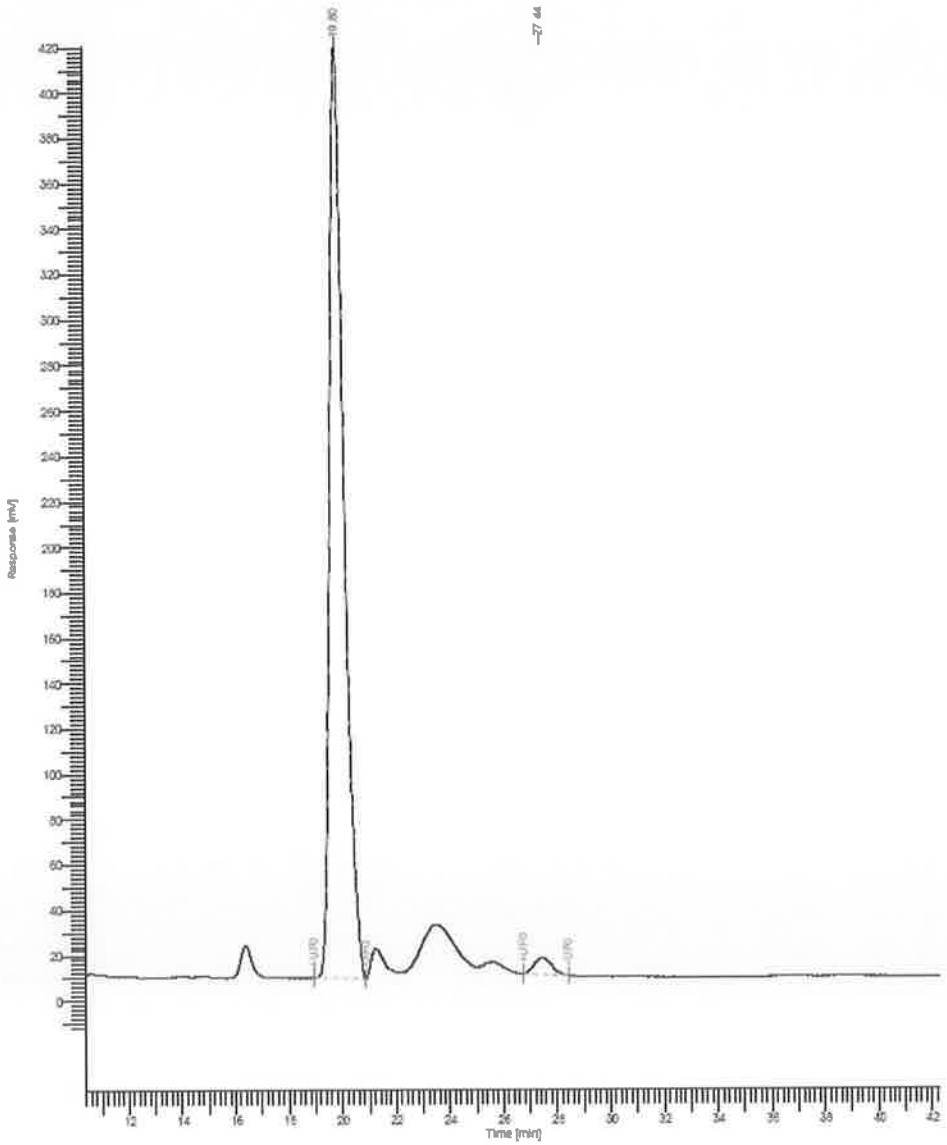
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		19.800	15270042.41	410522.41	97.94	97.94			*MM	15.2700	15.2700
2		27.441	321314.13	7453.39	2.06	2.06			*MM	0.3213	0.3213
			15591356.55	417975.80	100.00	100.00				15.5914	15.5914

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound *ent*-2.20c

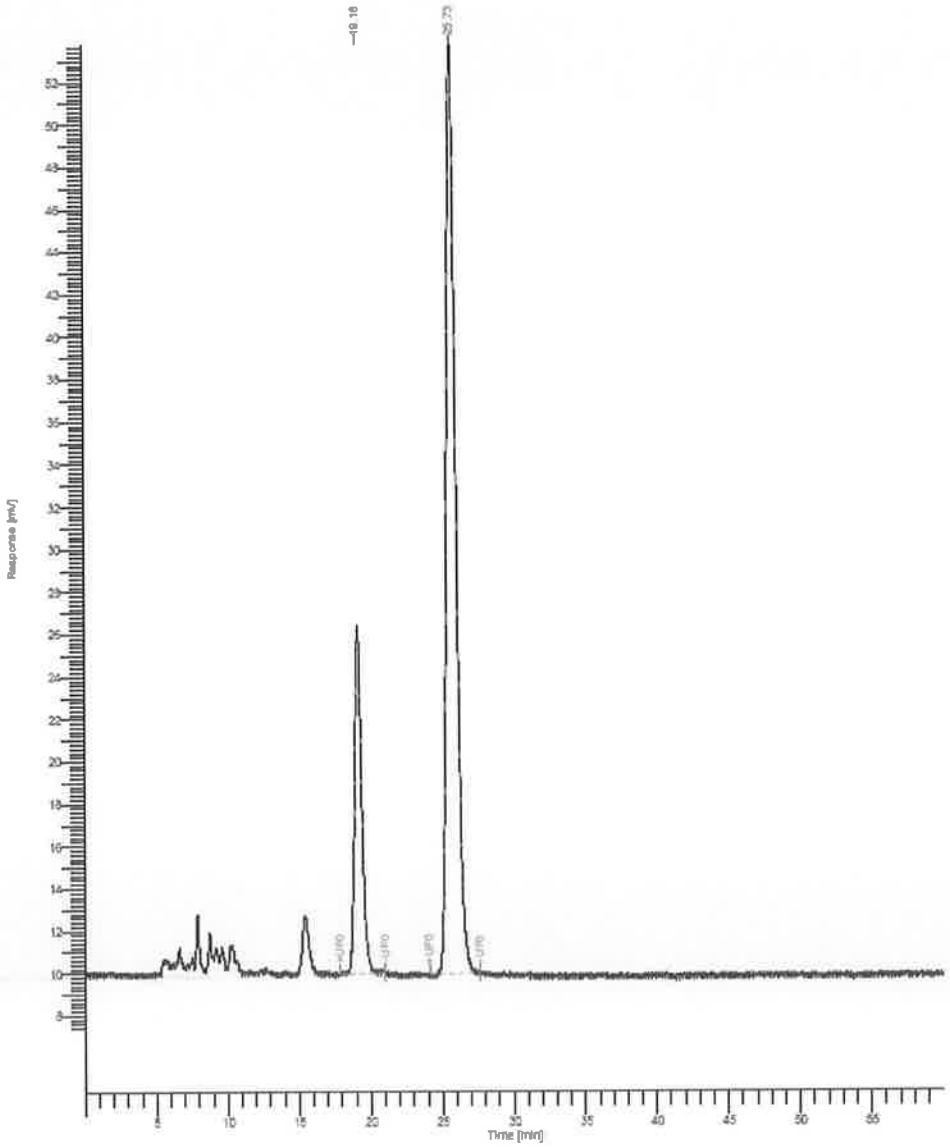
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		19.162	565300.00	16389.79	22.28	22.28			*MM	0.5653	0.5653
2		25.725	1971732.83	43806.84	77.72	77.72			*MM	1.9717	1.9717
			2537032.83	60196.62	100.00	100.00				2.5370	2.5370

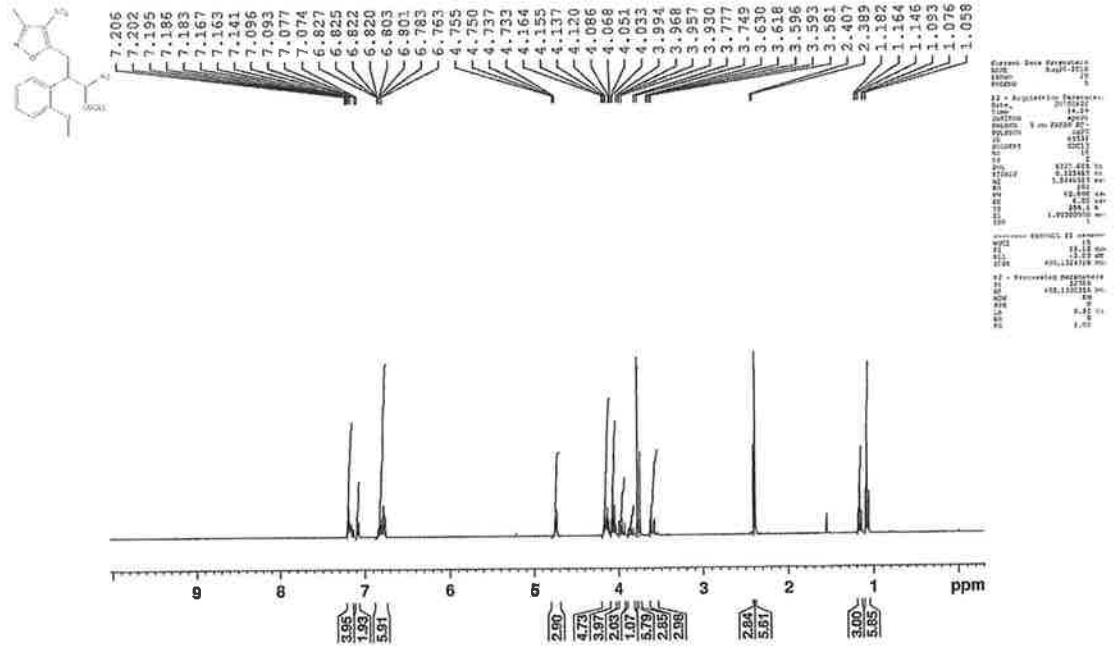
Missing Component Report

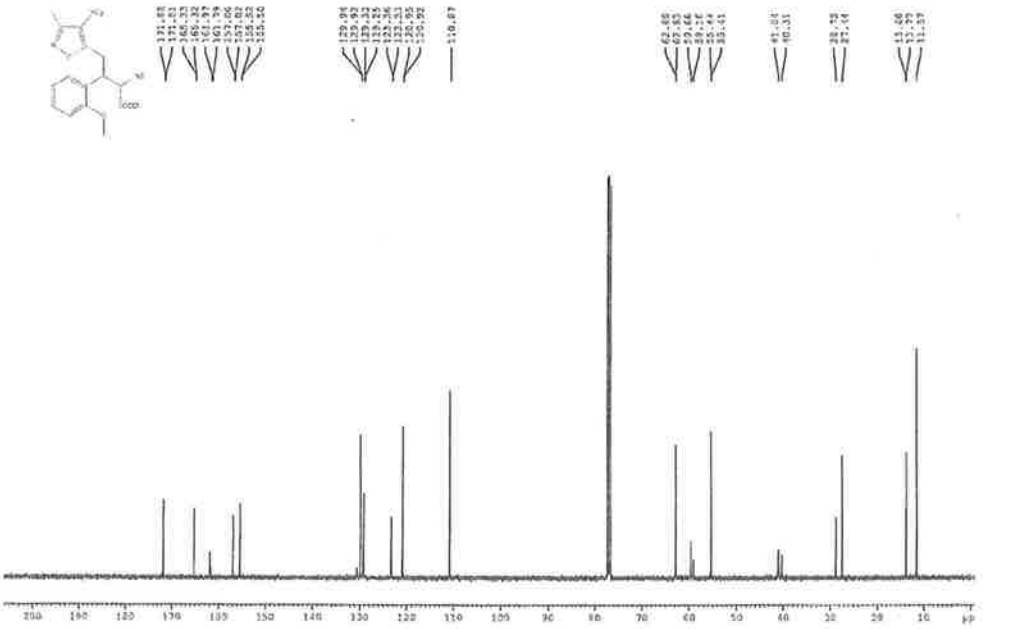
Component	Expected Retention (Calibration File)

All components were found



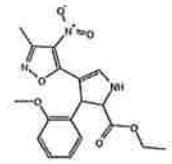
Compound 2.19d

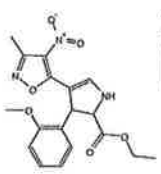




Compound 2.20d

Parameter	Value
Solvent	CDCl3
Temperature	29.0
Spectrometer Frequency	300.07





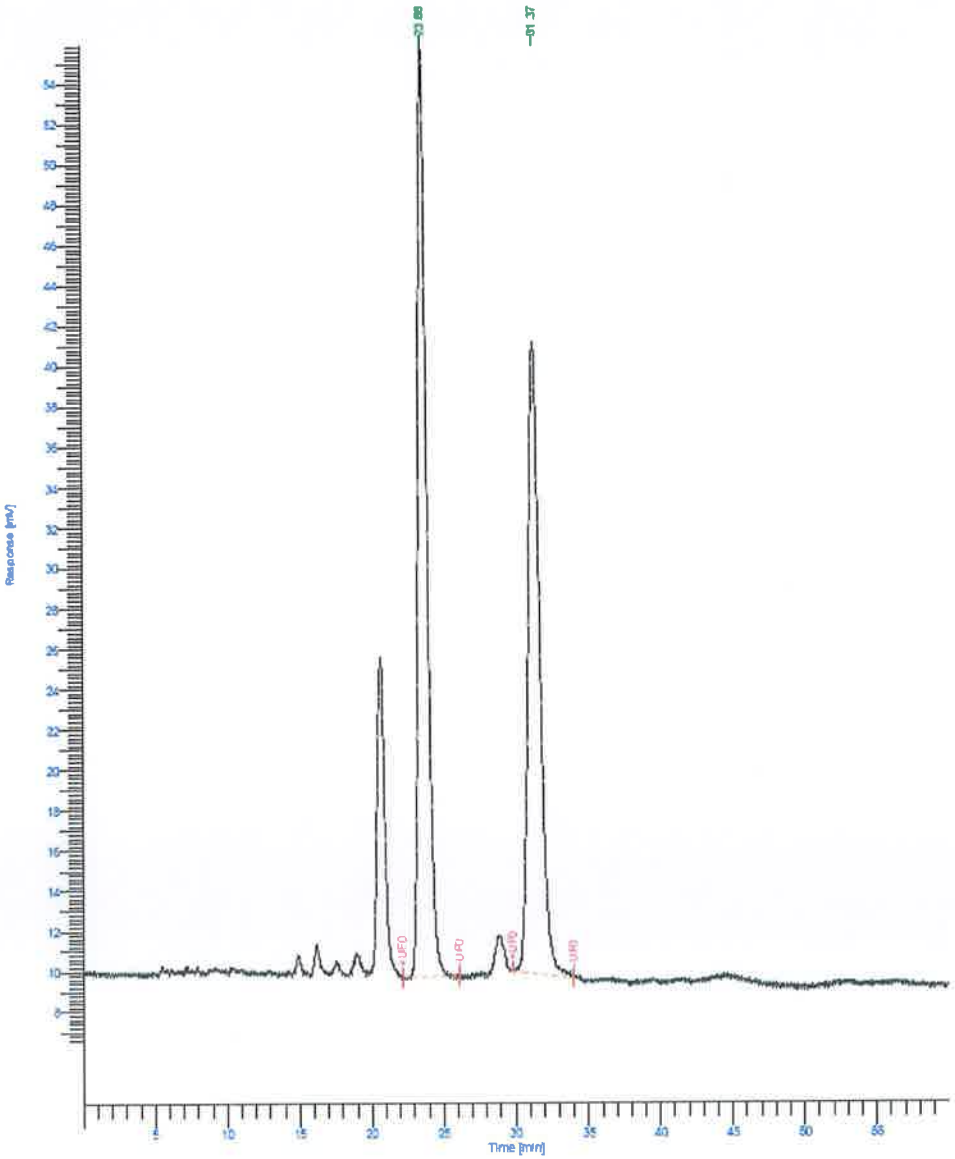
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		23.665	1950059.90	46182.65	52.45	52.45			*MM	1.9501	1.9501
2		31.372	1767607.12	31337.73	47.55	47.55			*MM	1.7676	1.7676
			3717667.02	77520.38	100.00	100.00				3.7177	3.7177

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20d

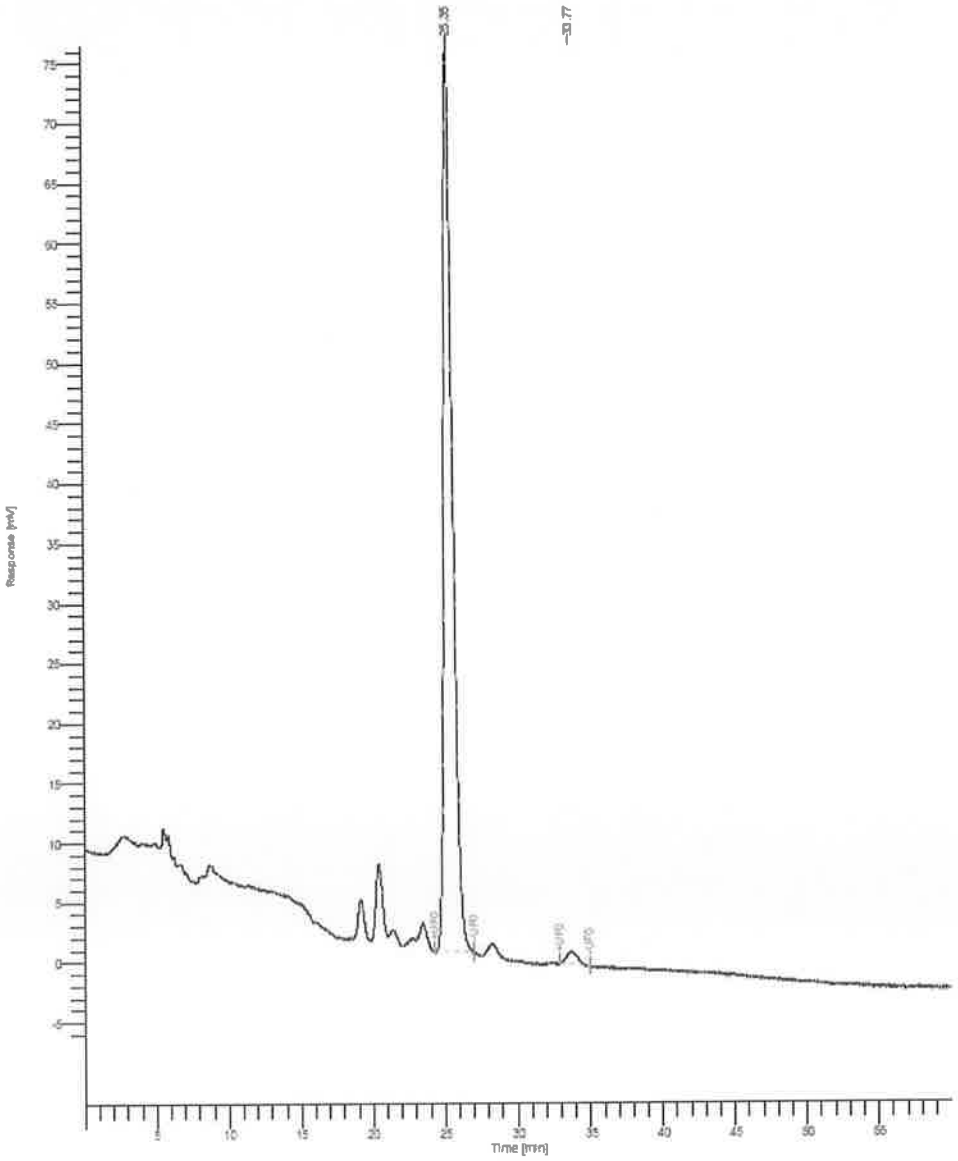
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		25.351	3254637.03	75587.79	98.35	98.35			*MM	3.2546	3.2546
2		33.770	54658.29	1153.18	1.65	1.65			*MM	0.0547	0.0547
			3309295.33	76740.98	100.00	100.00				3.3093	3.3093

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound *ent*-2.20d

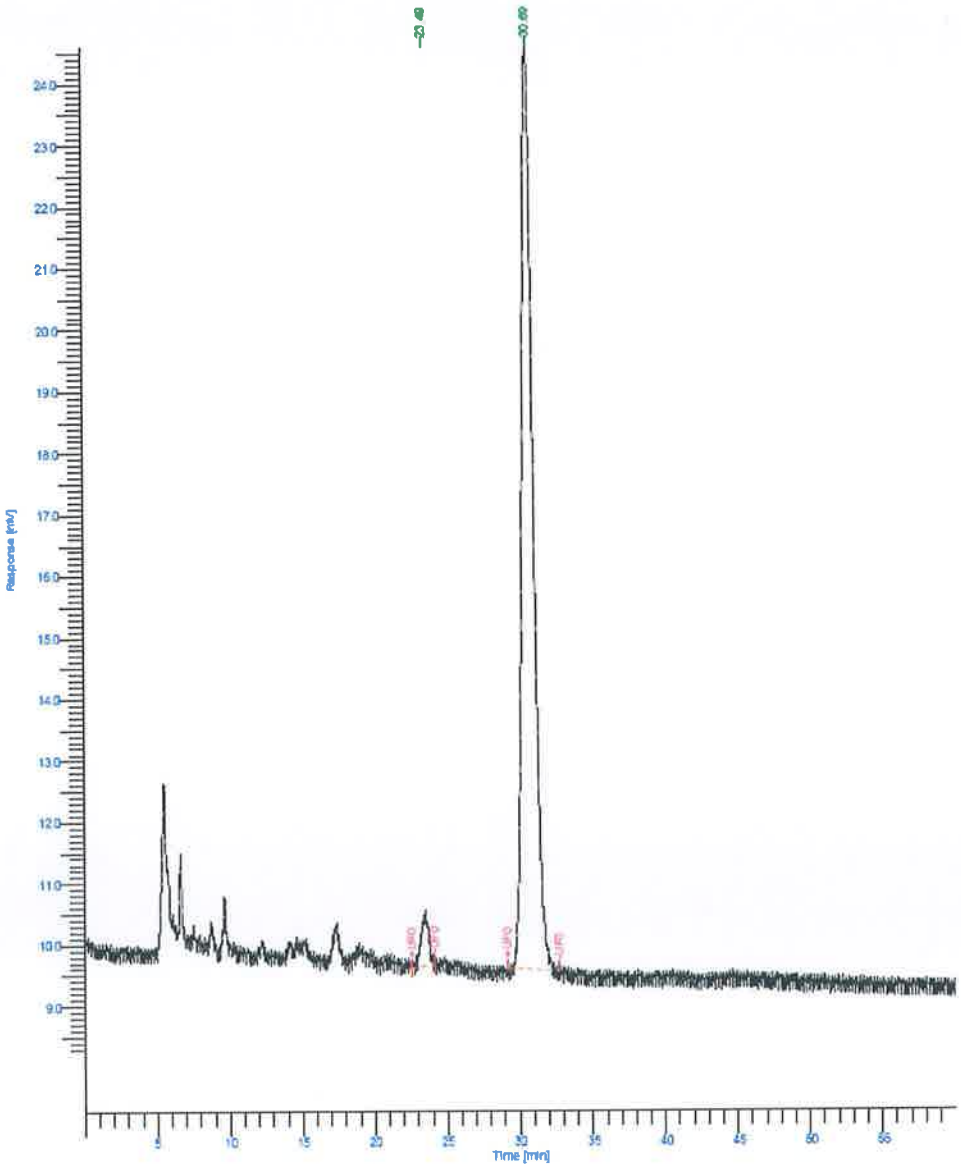
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		23.489	31747.92	907.57	3.79	3.79			*MM	0.0317	0.0317
2		30.690	806789.51	15012.95	96.21	96.21			*MM	0.8068	0.8068
			838537.43	15920.51	100.00	100.00				0.8385	0.8385

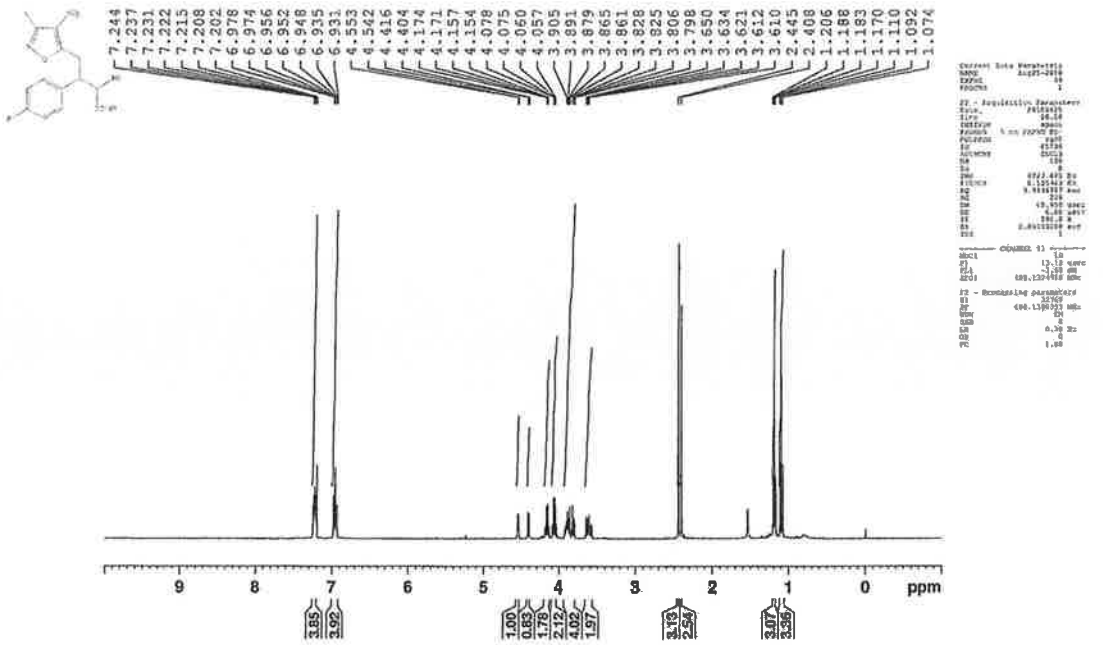
Missing Component Report

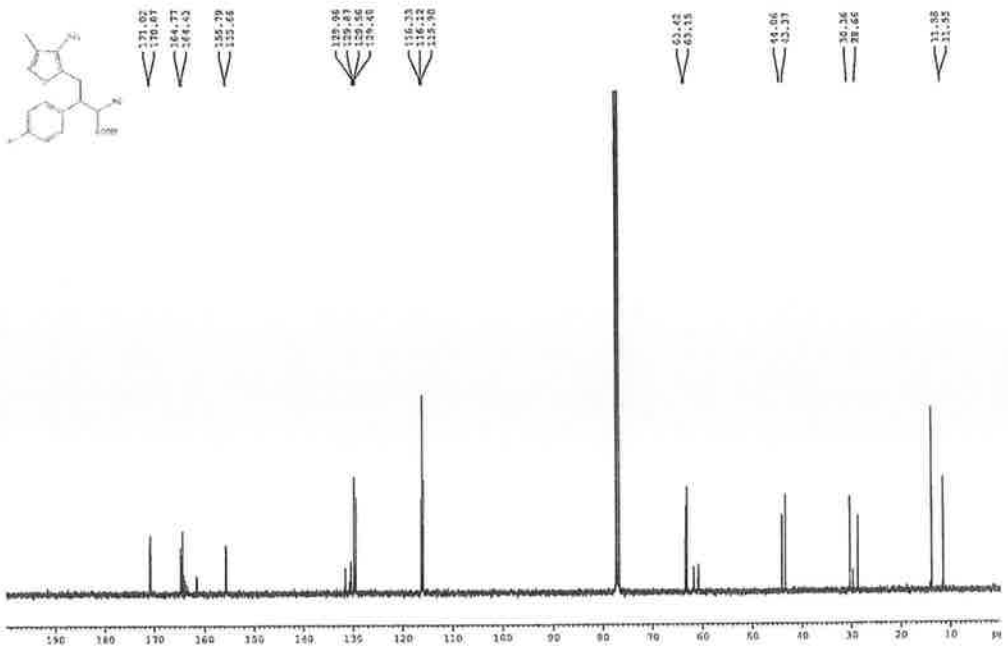
Component	Expected Retention (Calibration File)

All components were found

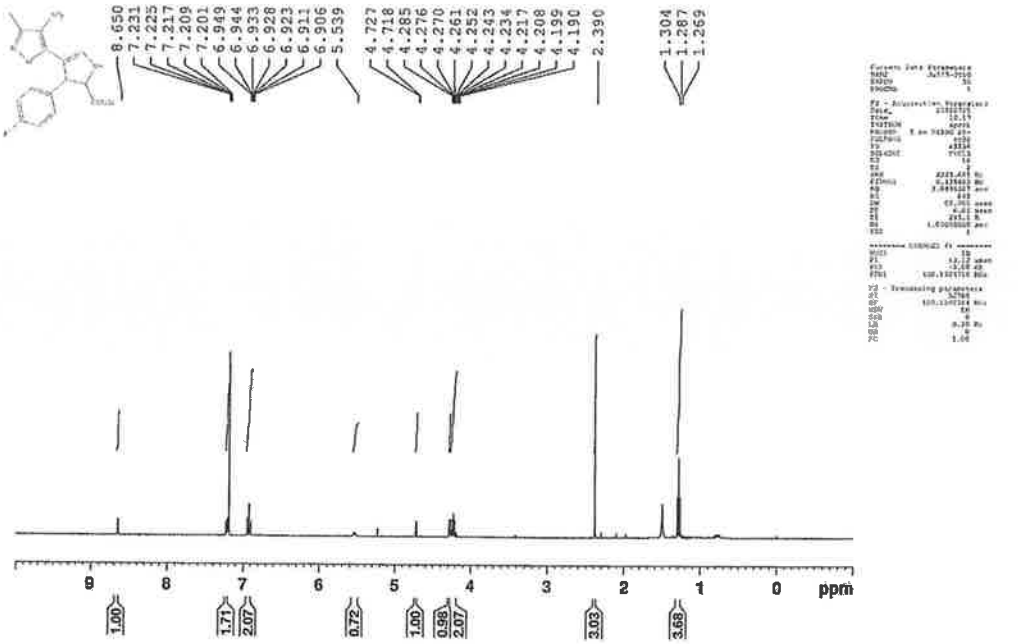


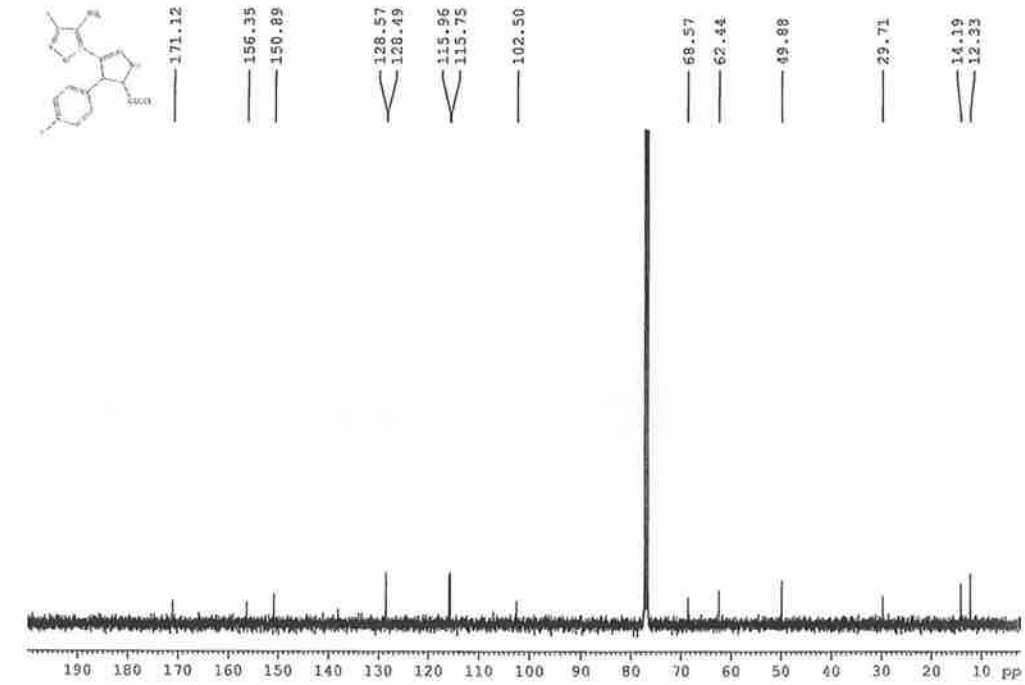
Compound 2.19e





Compound 2.20e





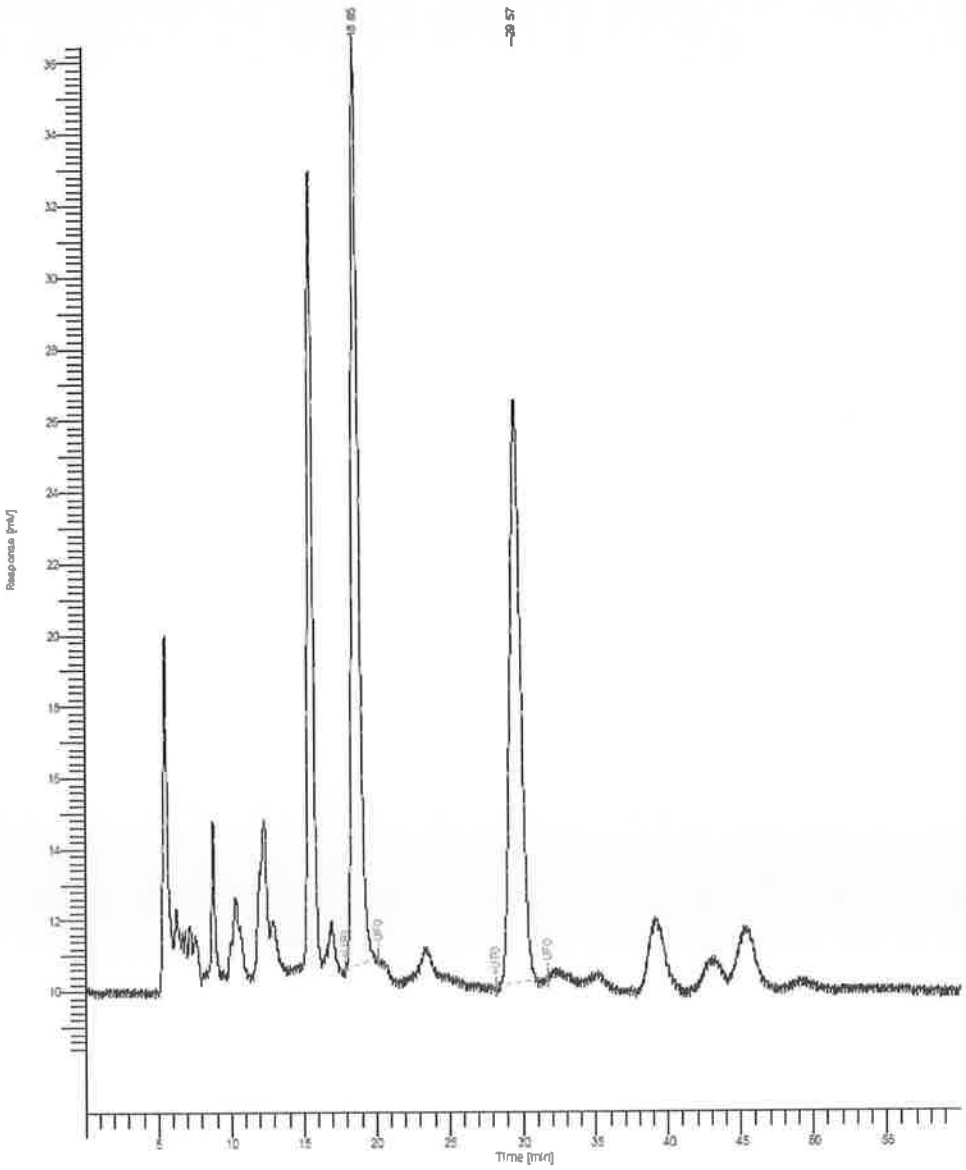
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.649	859178.47	25737.59	50.85	50.85			MM	0.8592	0.8592
2		29.568	830290.64	16330.19	49.15	49.15			MM	0.8303	0.8303
			1689469.10	42067.78	100.00	100.00				1.6895	1.6895

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20e

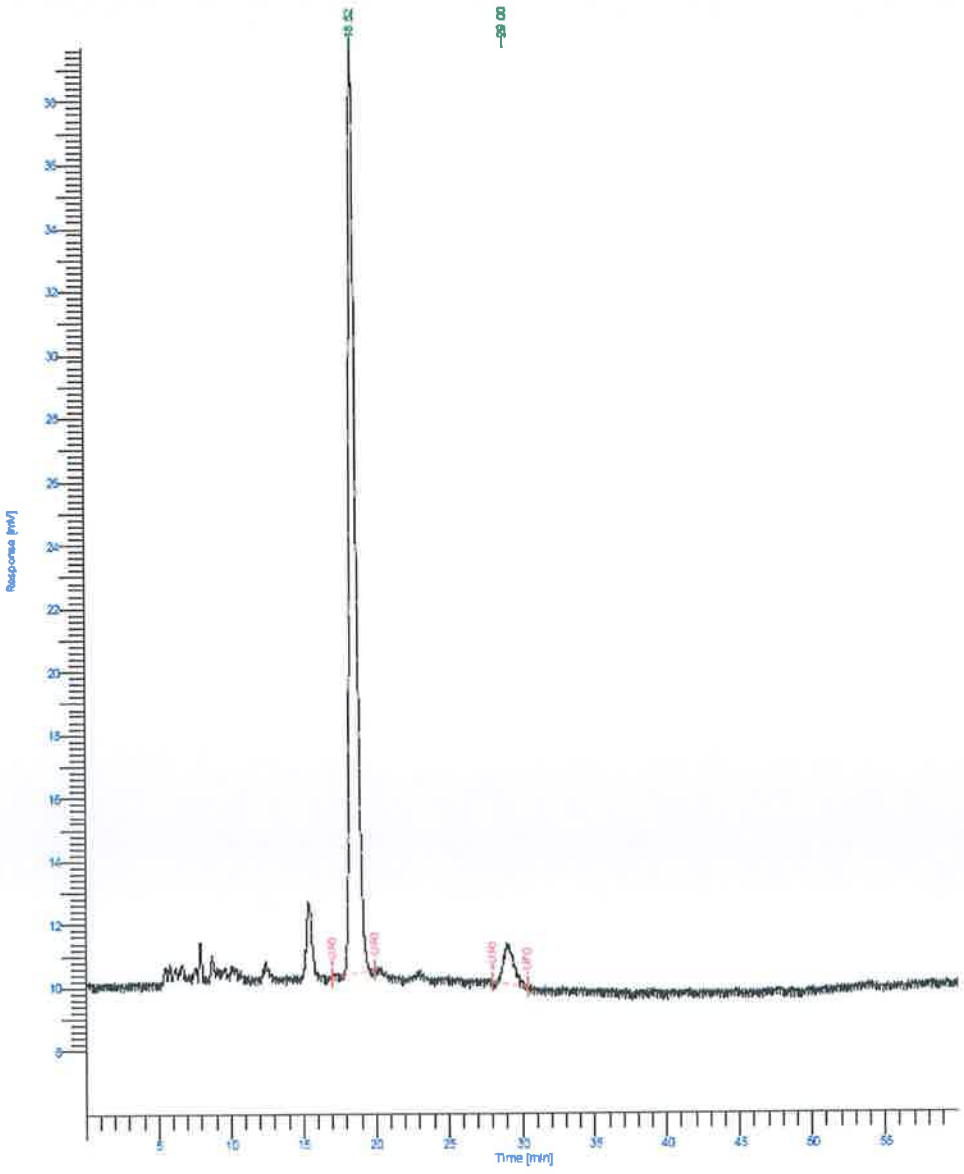
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.524	938629.53	29258.88	93.93	93.93			*MM	0.9386	0.9386
2		29.003	60691.81	1283.06	6.07	6.07			*MM	0.0607	0.0607
			999321.34	30541.95	100.00	100.00				0.9993	0.9993

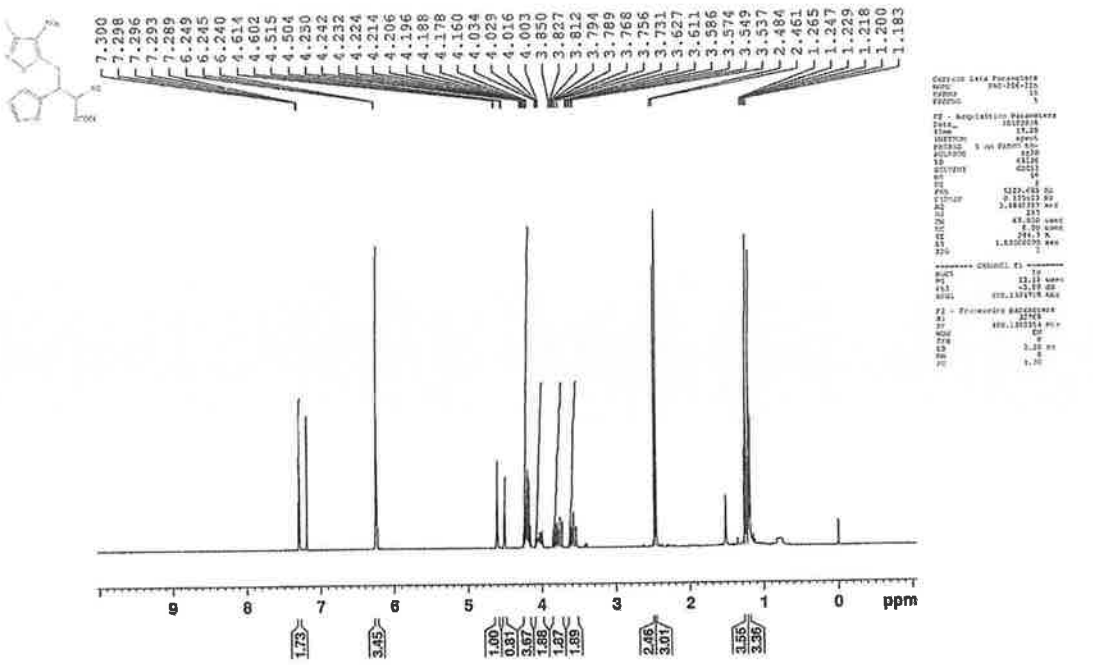
Missing Component Report

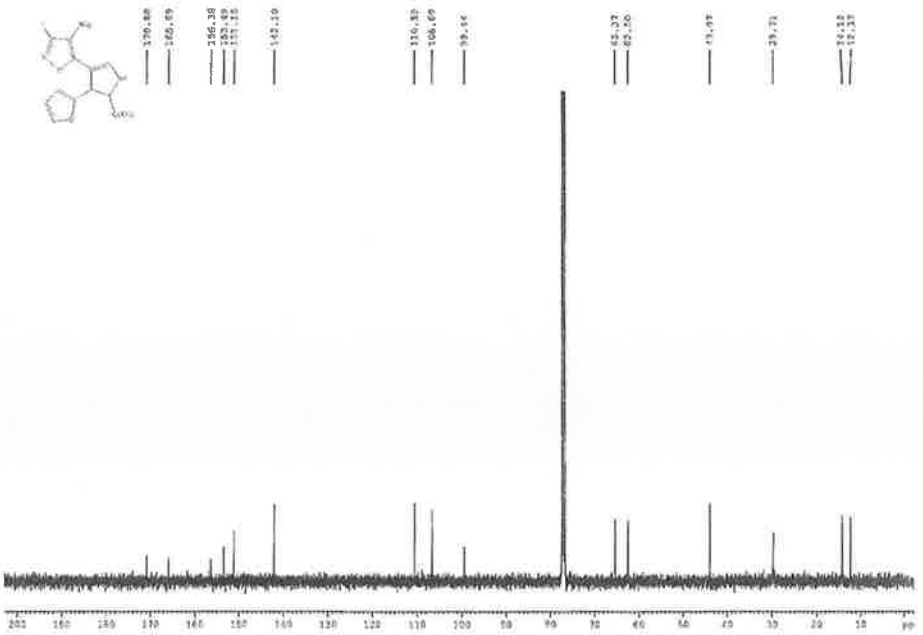
Component	Expected Retention (Calibration File)

All components were found

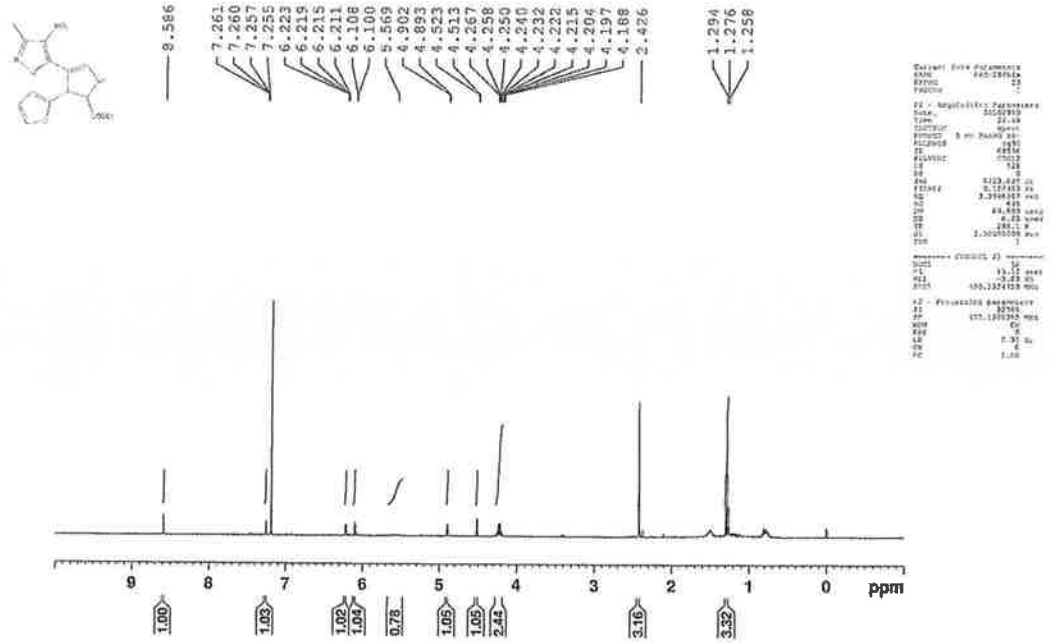


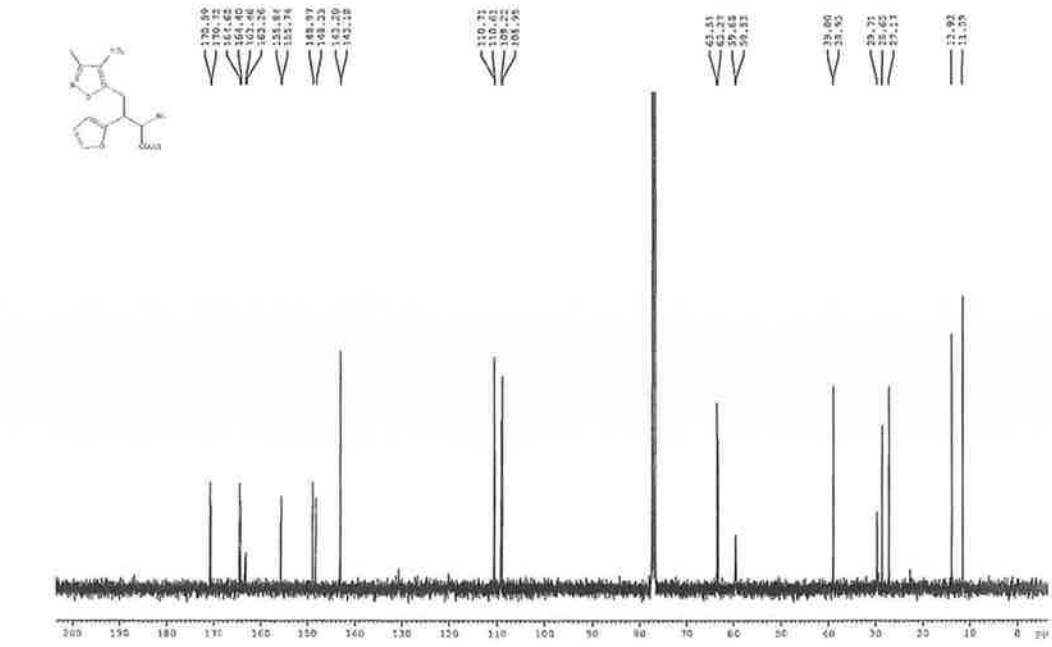
Compound 2.19f





Compound 2.20f





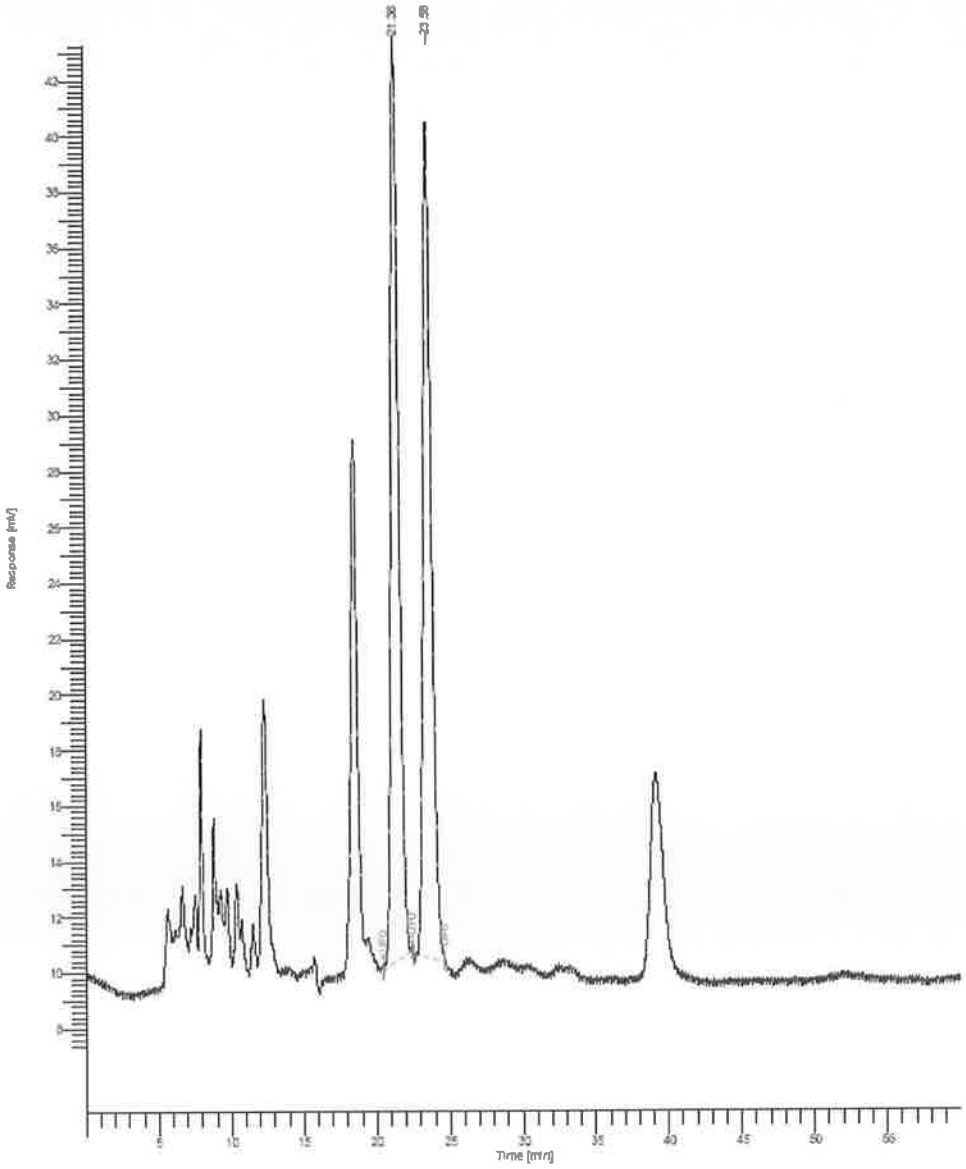
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		21.362	1203330.75	32873.89	50.25	50.25			*MM	1.2033	1.2033
2		23.577	1191576.34	29951.41	49.75	49.75			*MM	1.1916	1.1916
			2394907.09	62825.31	100.00	100.00				2.3949	2.3949

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20f

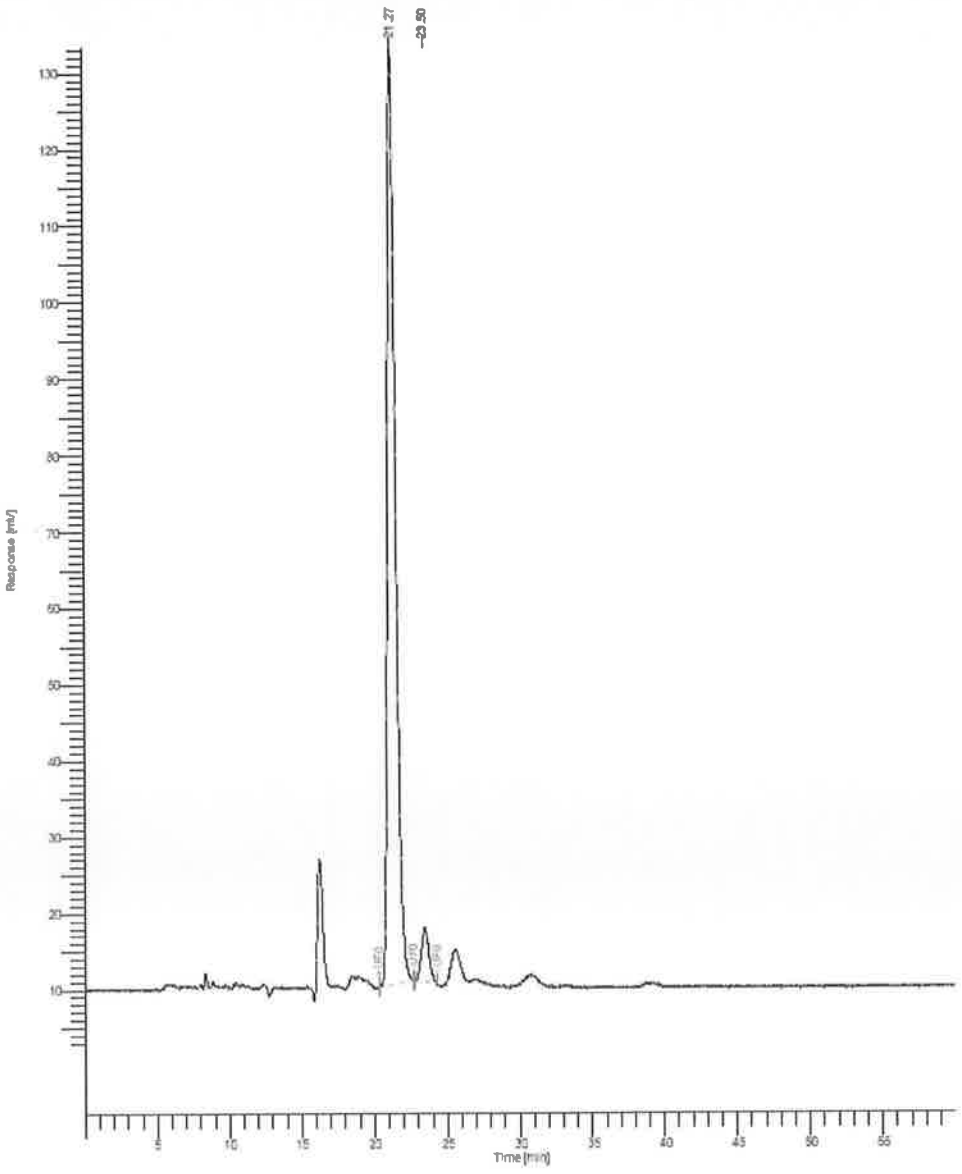
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		21.267	4587933.09	122703.77	94.61	94.61			*MM	4.5879	4.5879
2		23.496	261452.20	7111.11	5.39	5.39			*MM	0.2615	0.2615
			4849385.29	129814.88	100.00	100.00				4.8494	4.8494

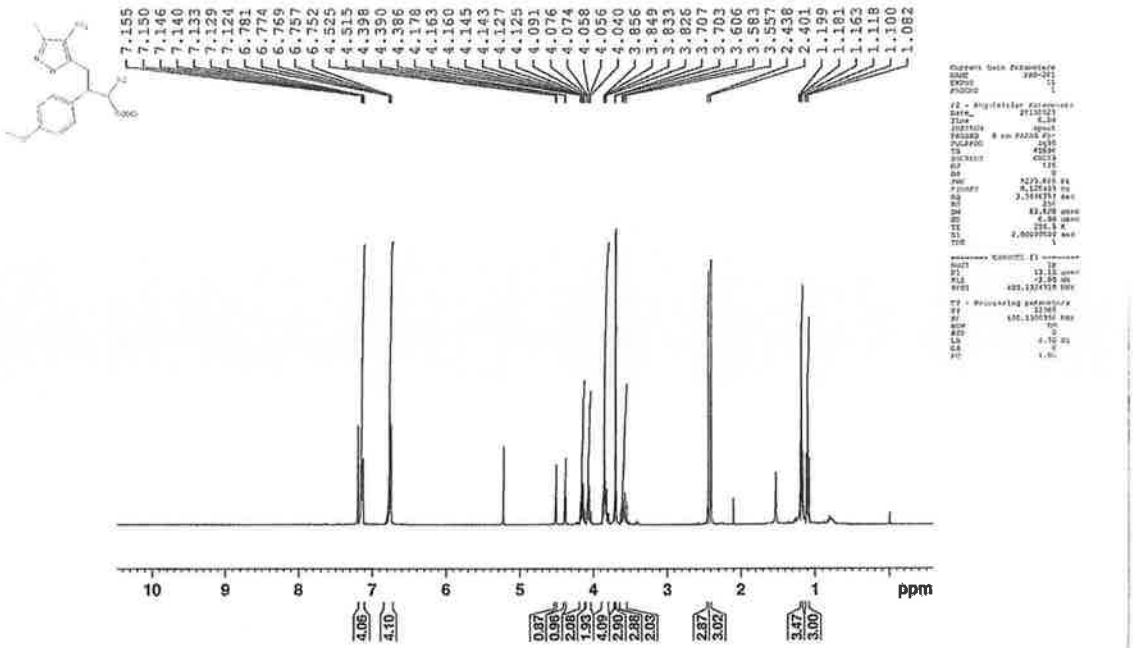
Missing Component Report

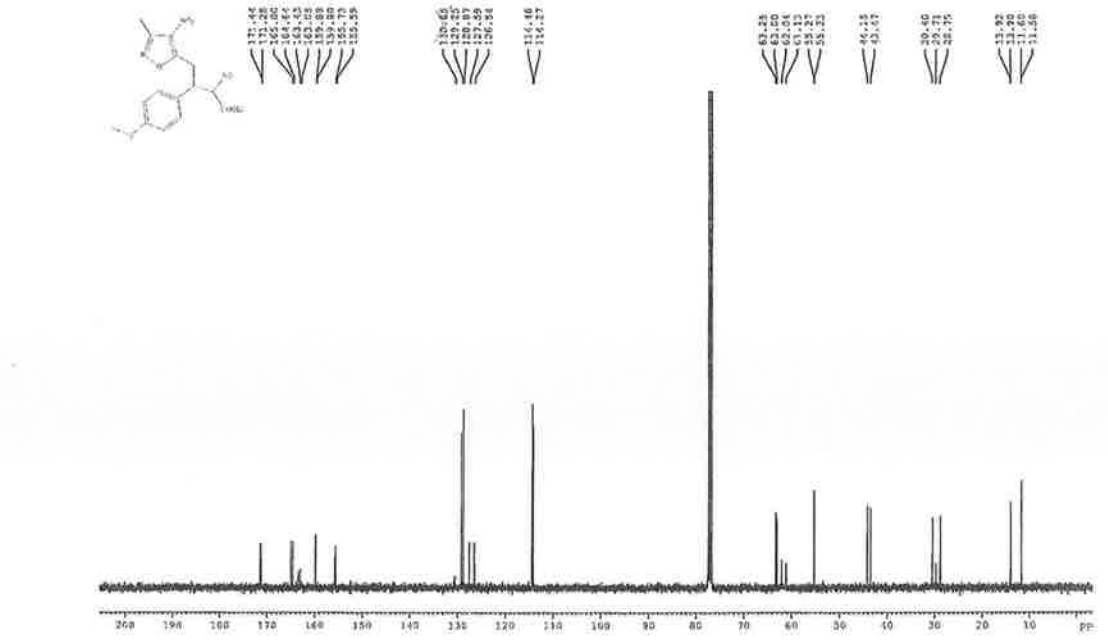
Component	Expected Retention (Calibration File)

All components were found

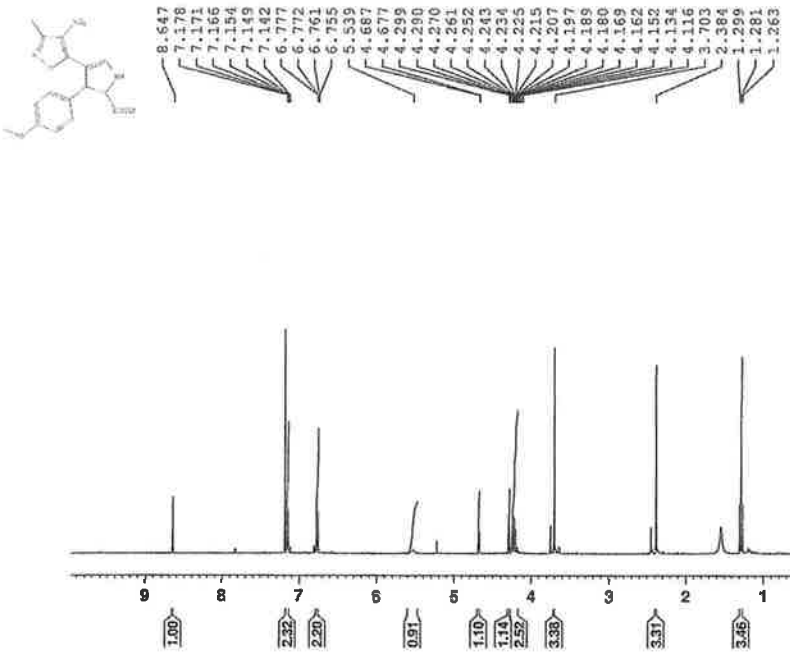


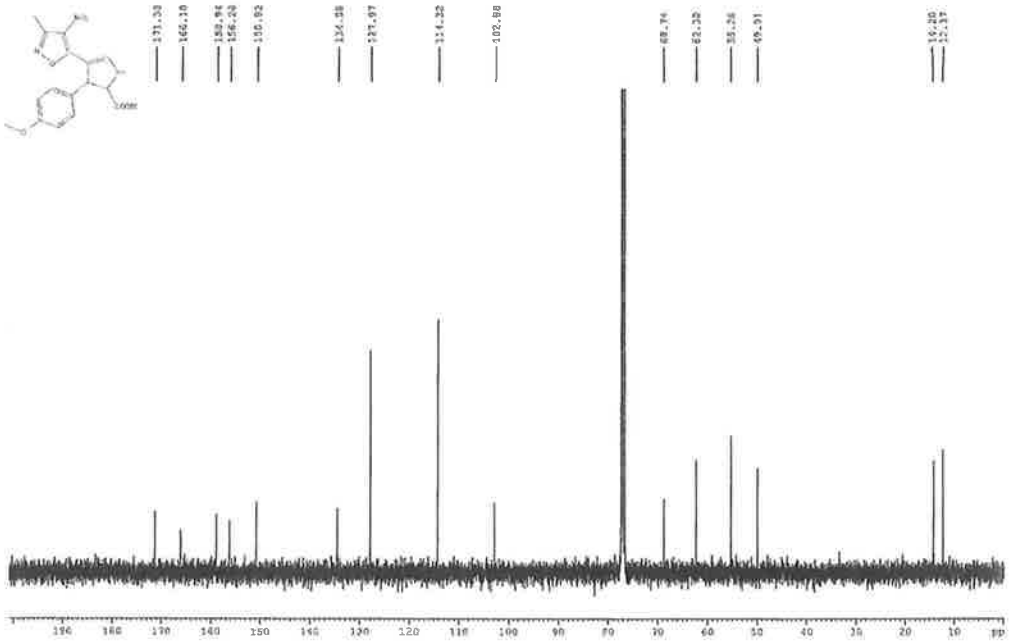
Compound 2.19g





Compound 2.20g

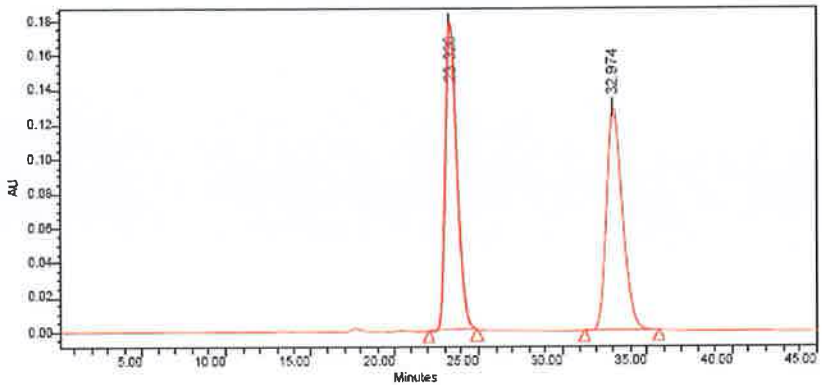




SAMPLE INFORMATION

Sample Name:	PAO-216-high	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	6/21/10 12:35:40 PM
Vial:	1	Acq. Method Set:	Chiralmiscela
Injection #:	1	Date Processed:	6/21/10 1:47:49 PM
Injection Volume:	10.00 ul	Processing Method:	HPLC
Run Time:	45.0 Minutes	Channel Name:	PDA Single 421.0 nm
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm

Auto-Scaled Chromatogram



Unknown Peak Results

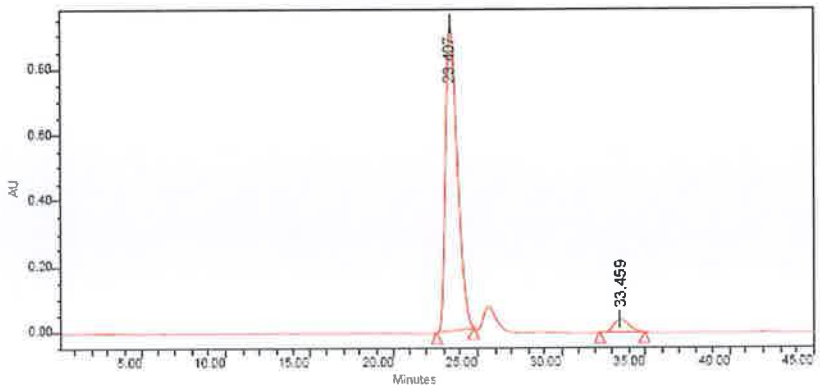
	Peak Type	RT	Area	% Area	Height
1	Unknown	23.326	8432092	49.80	177606
2	Unknown	32.974	8499219	50.20	128809

Compound 2.20g

SAMPLE INFORMATION

Sample Name:	PAO-239-2	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	6/21/10 11:48:37 AM
Vial:	3	Acq. Method Set:	Chiralmiscela
Injection #:	1	Date Processed:	6/21/10 1:52:35 PM
Injection Volume:	10.00 ul	Processing Method:	HPLC
Run Time:	45.0 Minutes	Channel Name:	PDA Single 421.0 nm
Sample Set Name:	PPDD	Proc. Chnl. Descr.:	PDA 254.0 nm

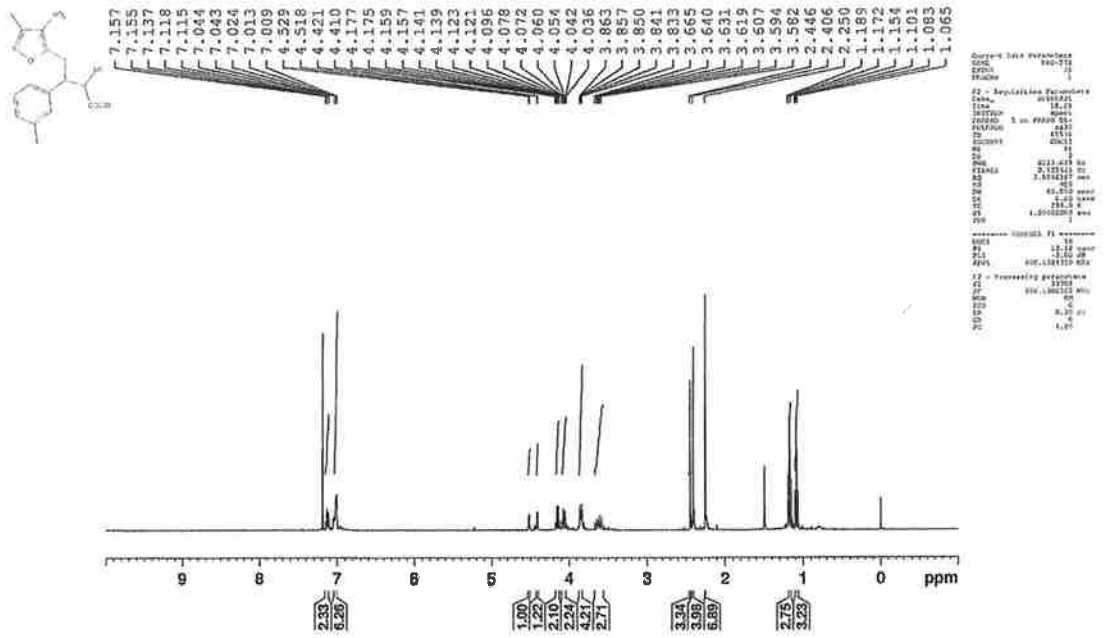
Auto-Scaled Chromatogram

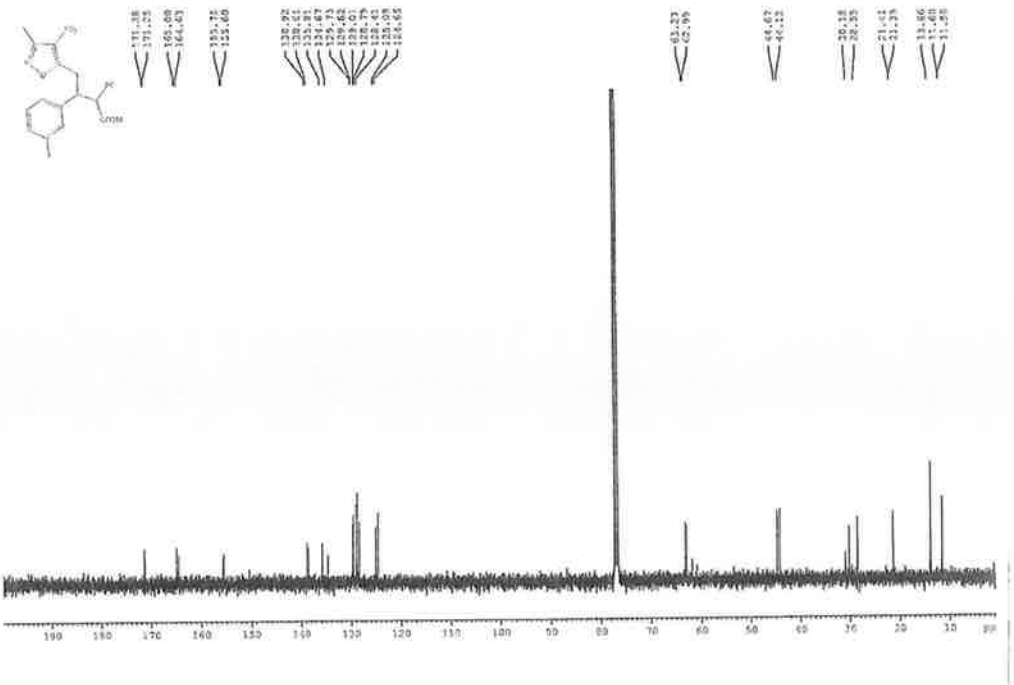


Unknown Peak Results

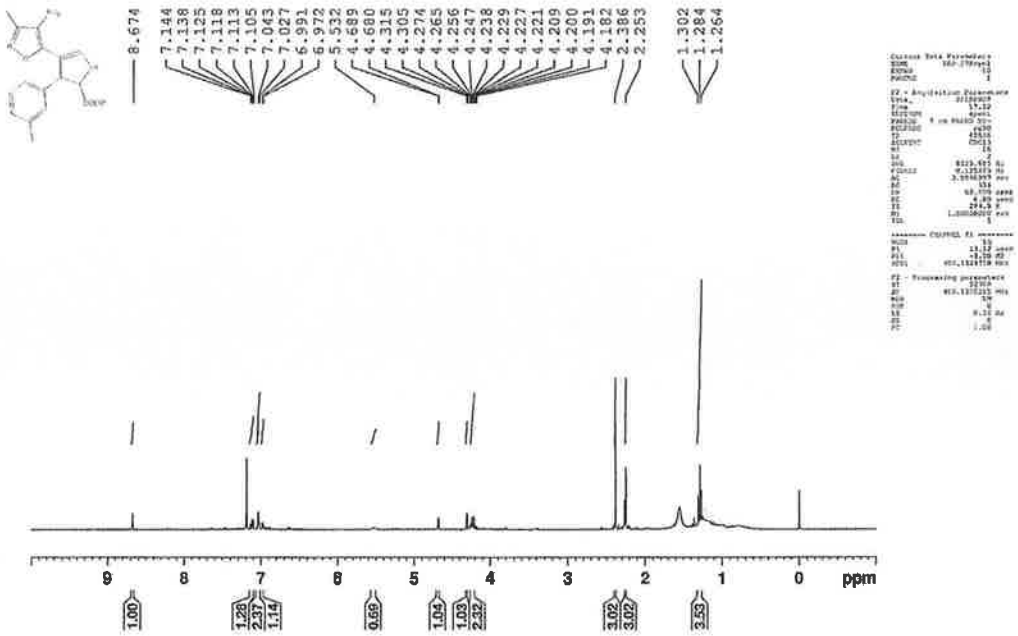
	Peak Type	RT	Area	% Area	Height
1	Unknown	23.407	45178895	94.57	931115
2	Unknown	33.459	2592819	5.43	39851

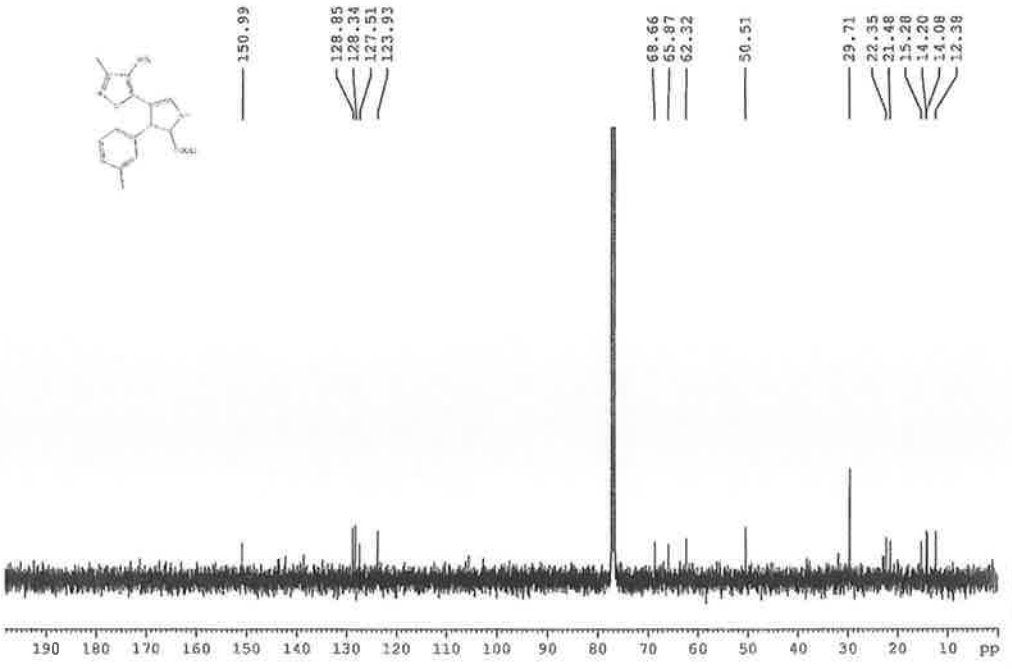
Compound 2.19h





Compound 2.20h





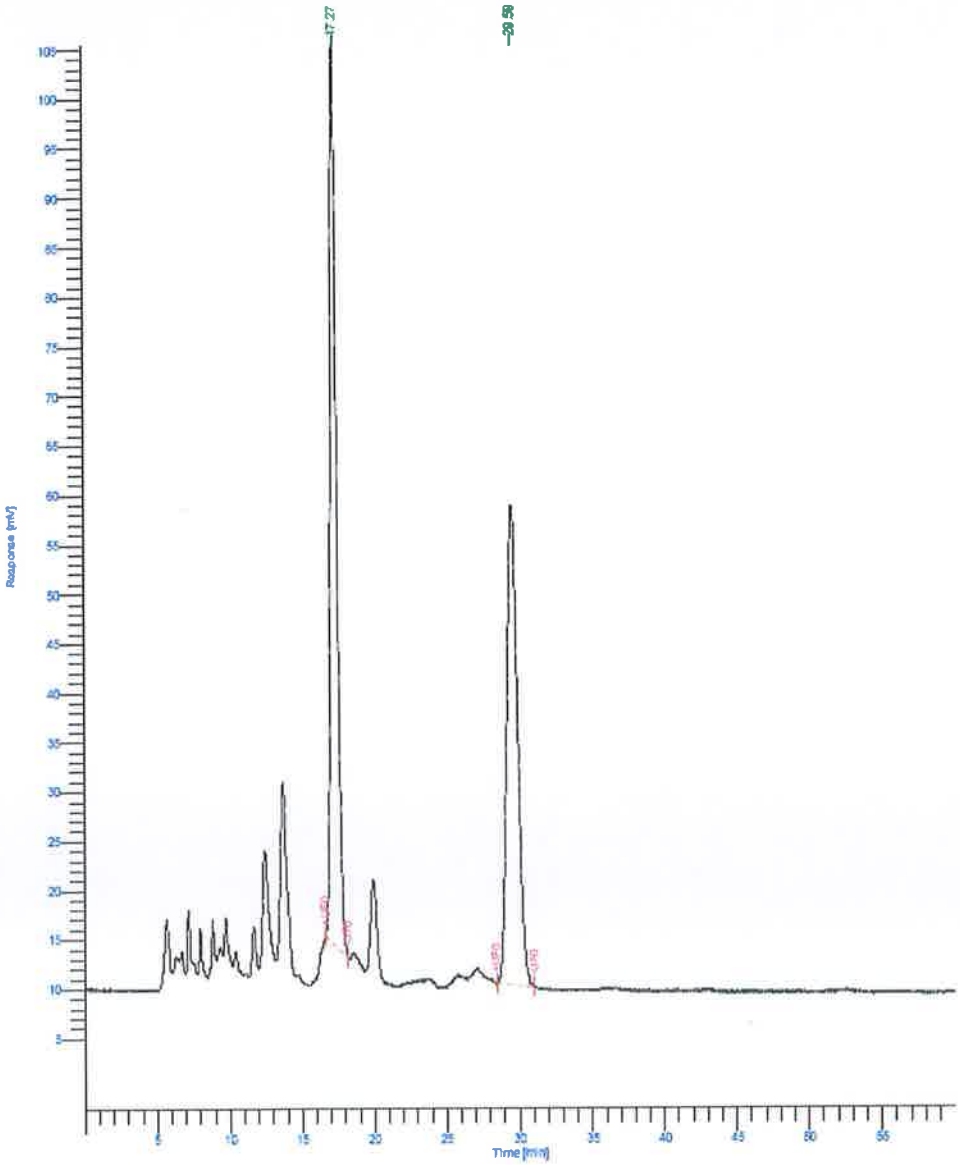
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		17.270	2752821.05	91034.11	52.80	52.80			*MM	2.7528	2.7528
2		29.590	2460912.88	48624.82	47.20	47.20			*MM	2.4609	2.4609
			5213733.93	139658.93	100.00	100.00				5.2137	5.2137

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20h

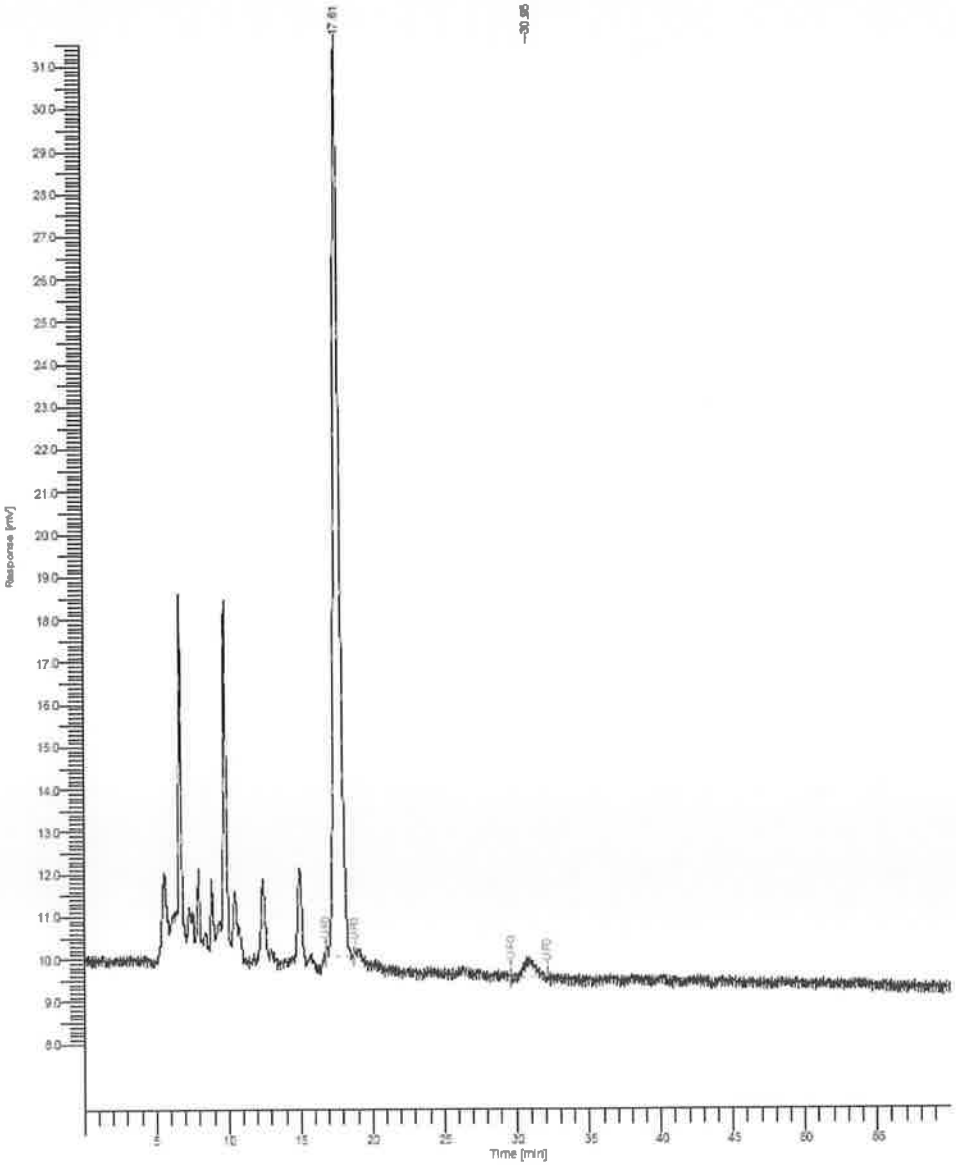
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		17.615	649869.84	21453.19	96.79	96.79			*MM	0.6499	0.6499
2		30.947	21519.22	457.76	3.21	3.21			*MM	0.0215	0.0215
			671389.06	21910.95	100.00	100.00				0.6714	0.6714

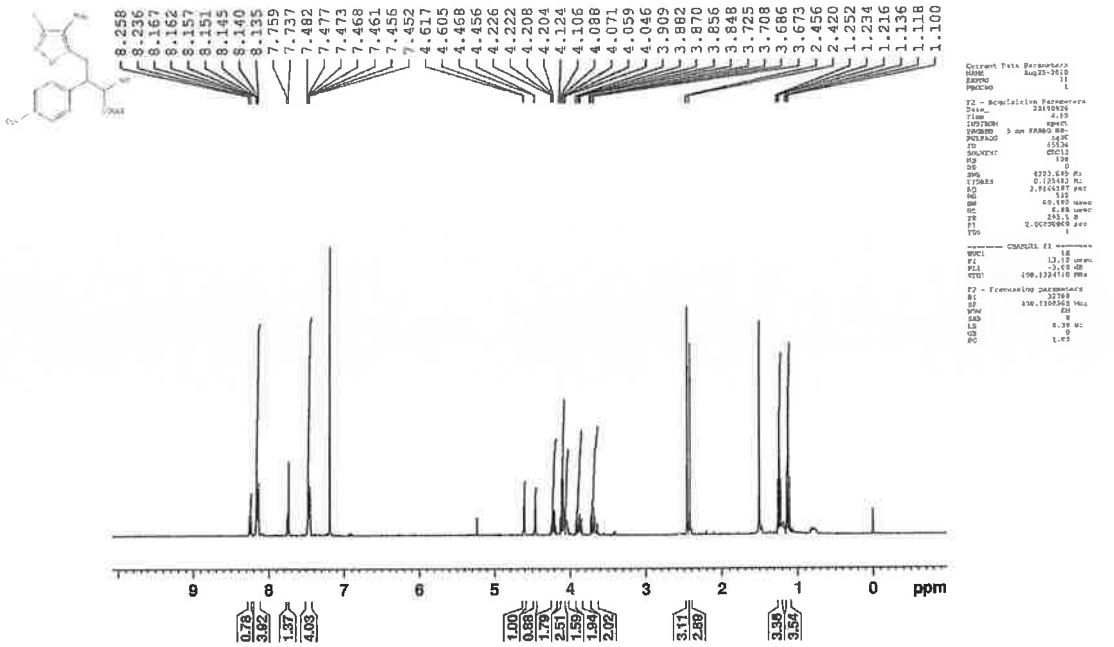
Missing Component Report

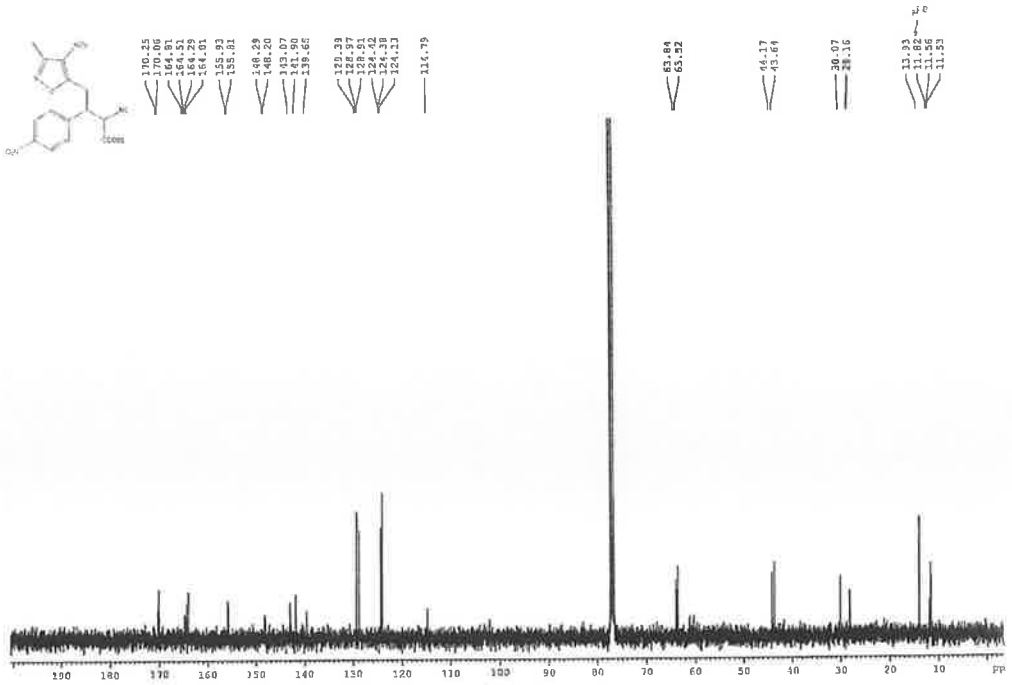
Component	Expected Retention (Calibration File)

All components were found

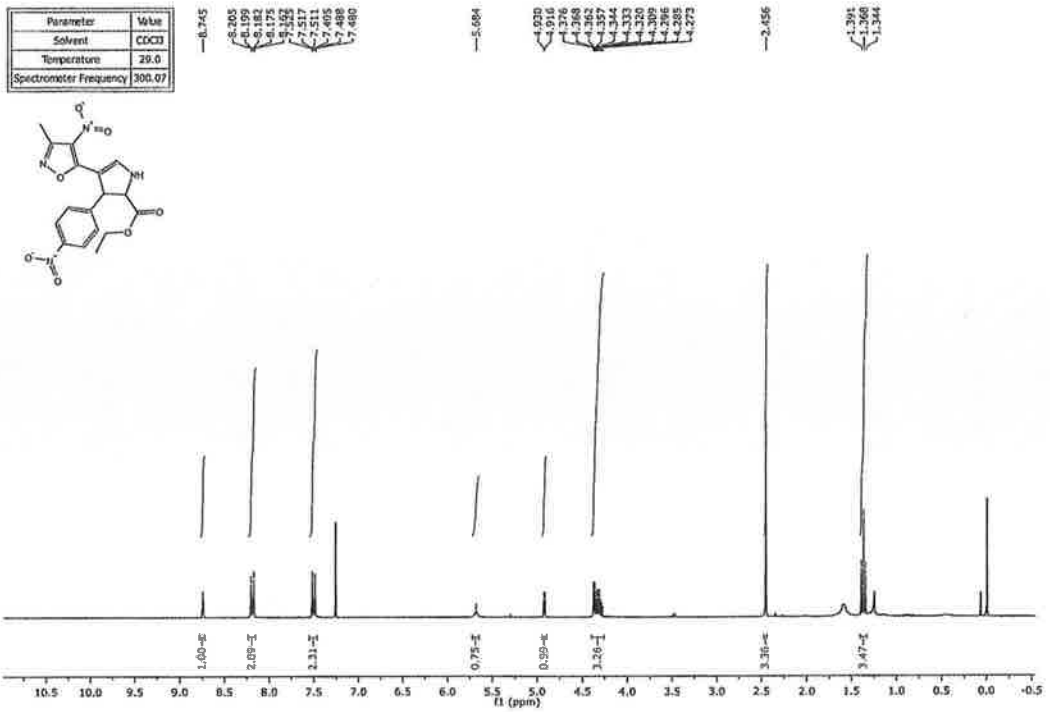


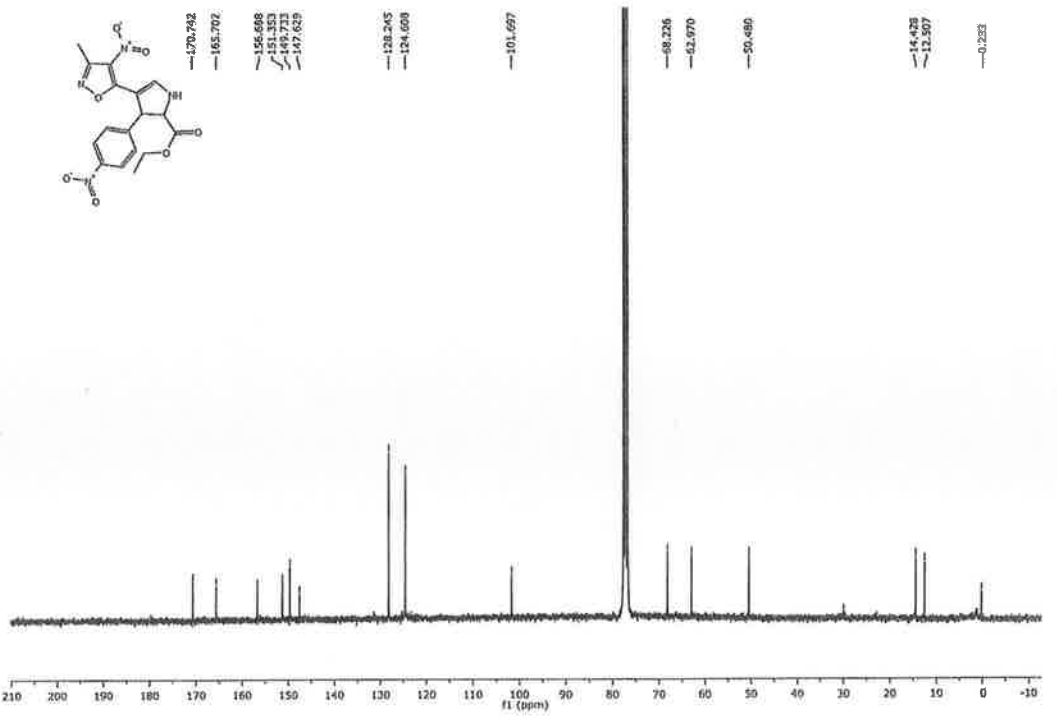
Compound 2.19i





Compound 2.20i





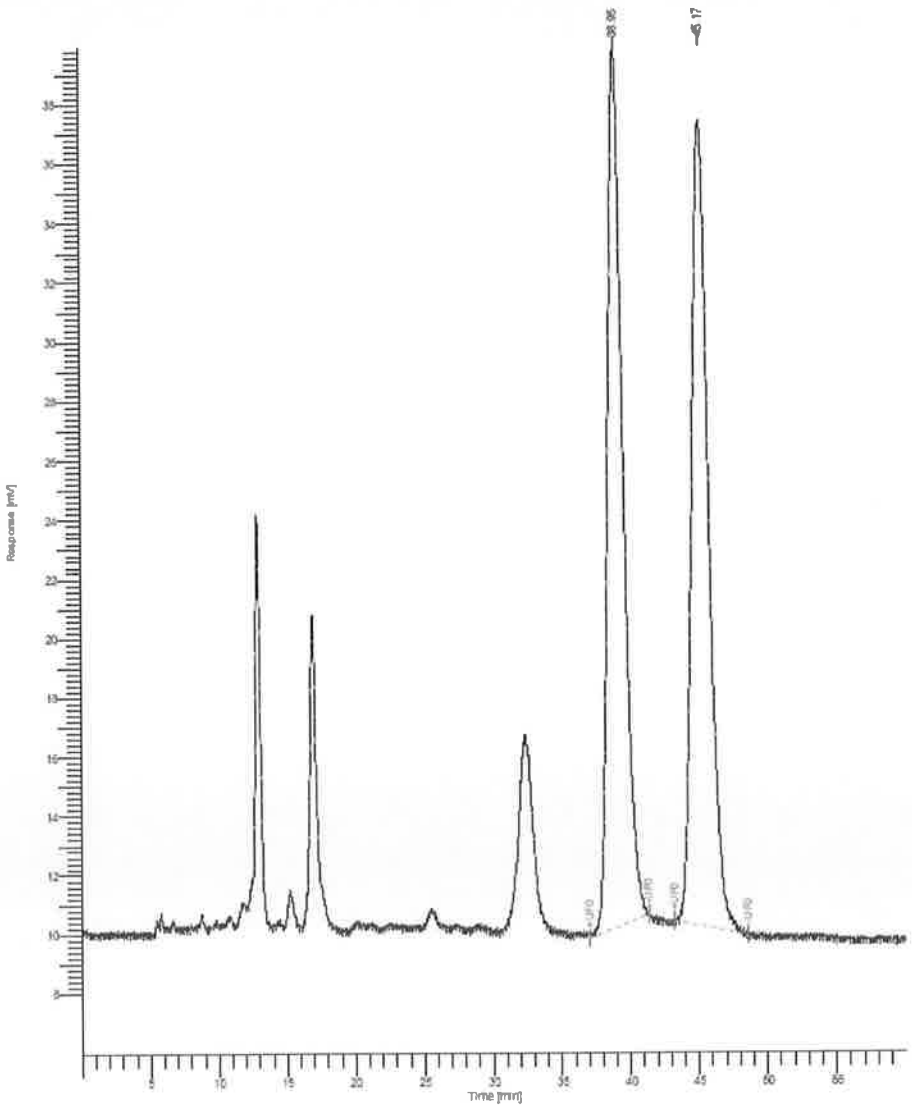
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		38.955	2298795.81	29737.68	49.79	49.79			*MM	2.2988	2.2988
2		45.166	2318266.75	27173.20	50.21	50.21			*MM	2.3183	2.3183
			4617062.56	56910.89	100.00	100.00				4.6171	4.6171

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20i

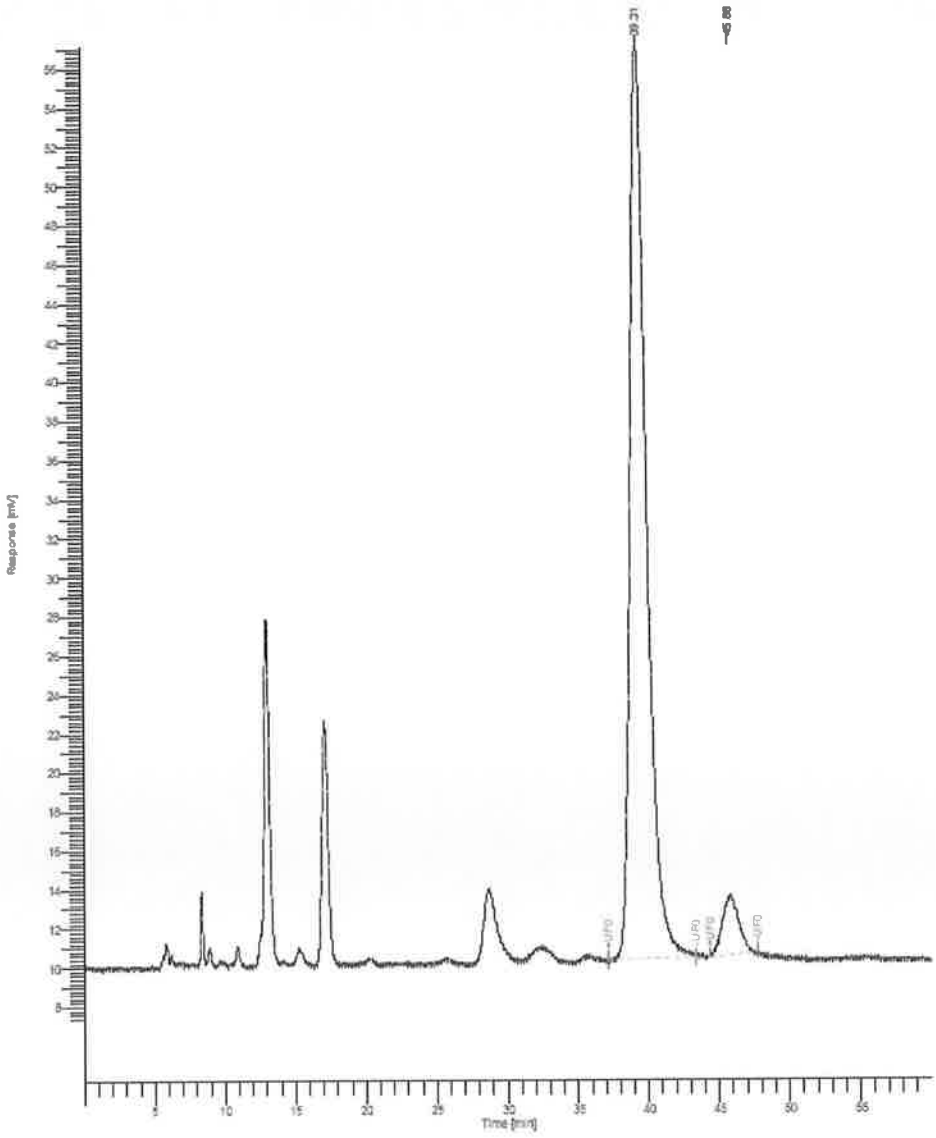
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		39.314	3818233.72	46749.54	93.89	93.89			'MM	3.8182	3.8182
2		45.877	248593.85	3066.21	6.11	6.11			'MM	0.2486	0.2486
			4066827.57	49815.75	100.00	100.00				4.0668	4.0668

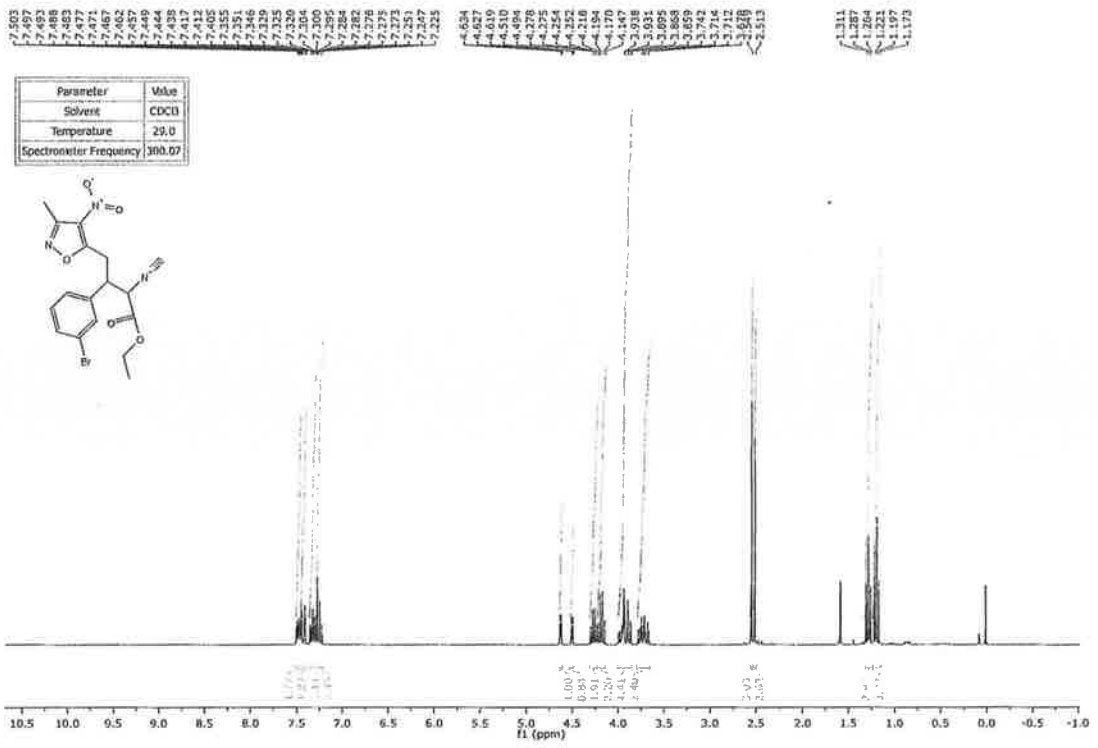
Missing Component Report

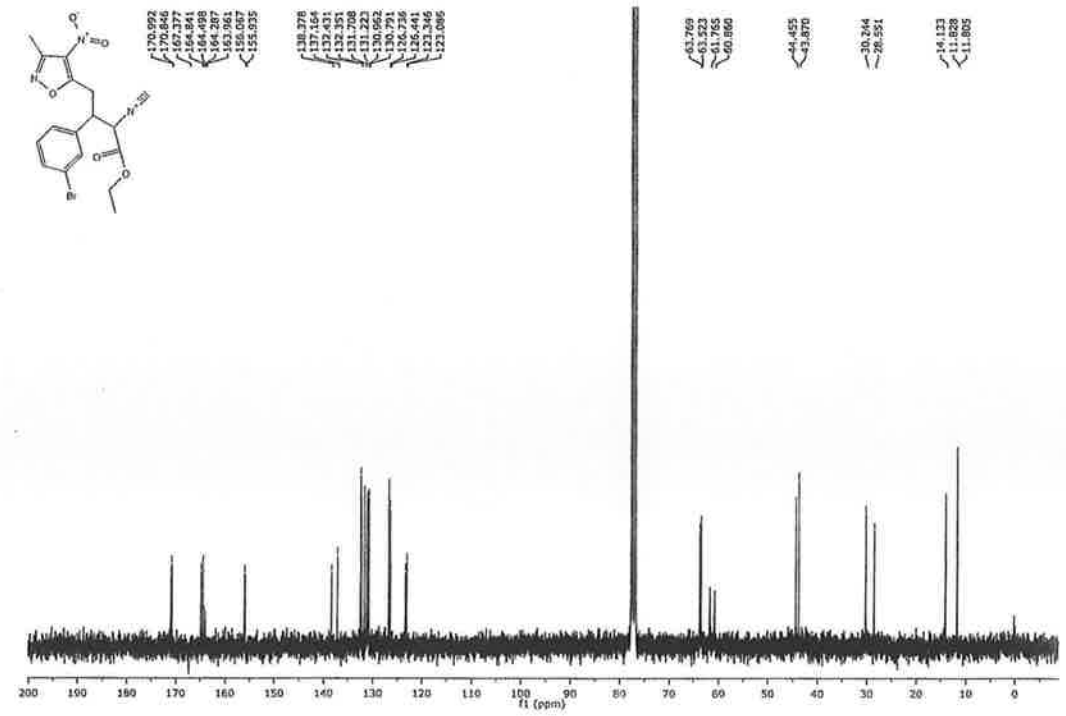
Component	Expected Retention (Calibration File)

All components were found

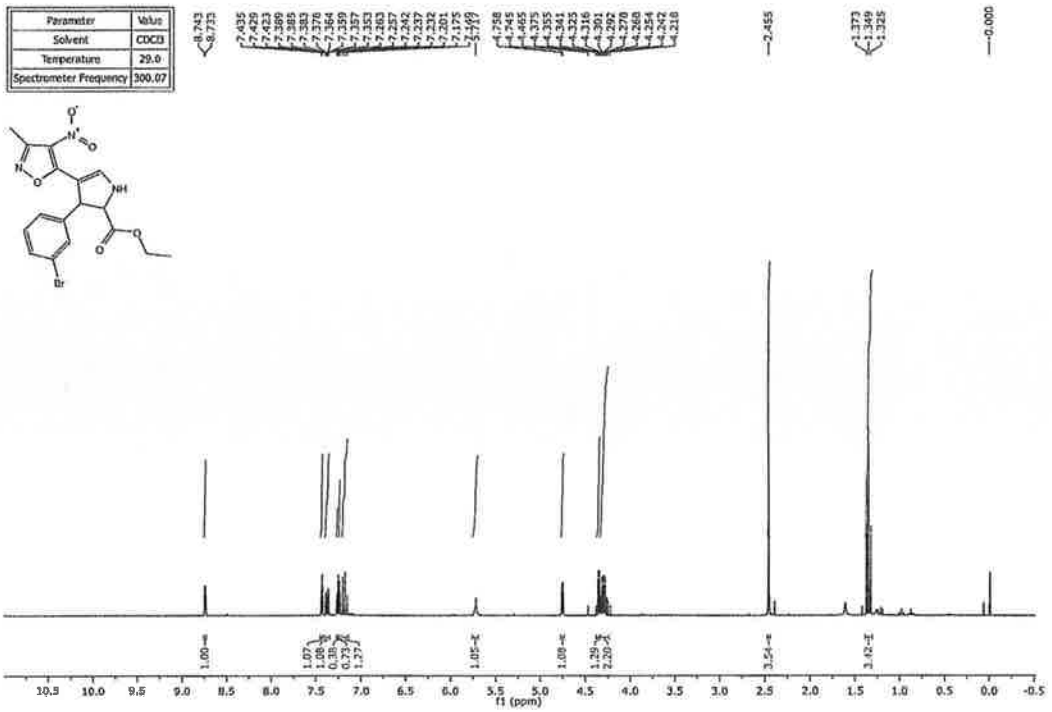


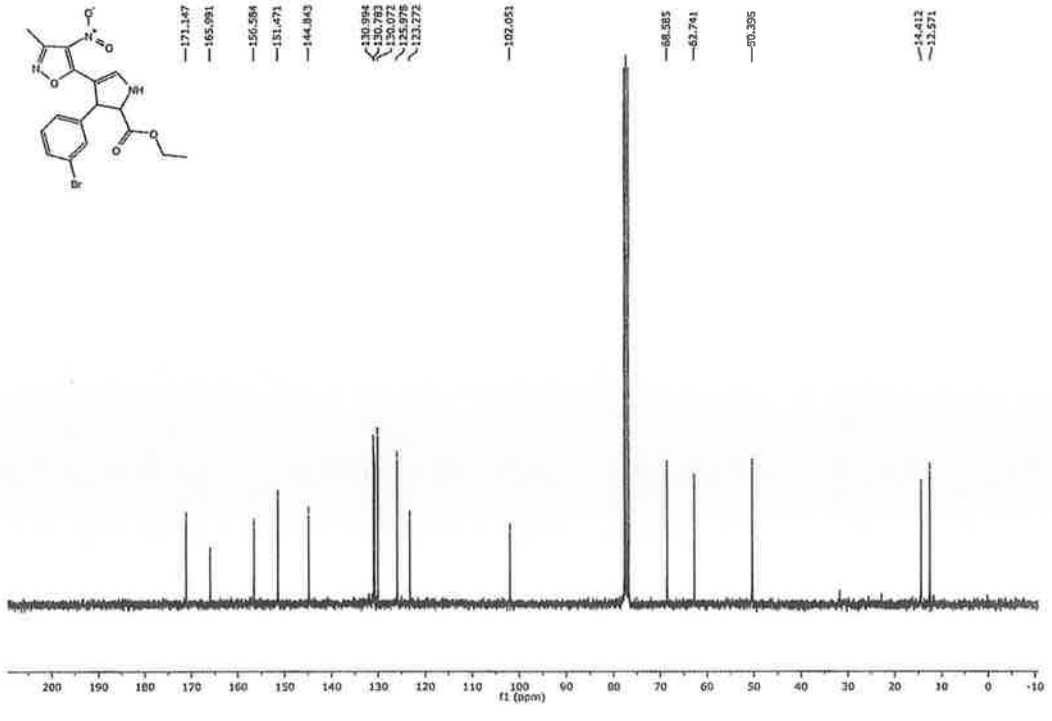
Compound 2.19j





Compound 2.20j





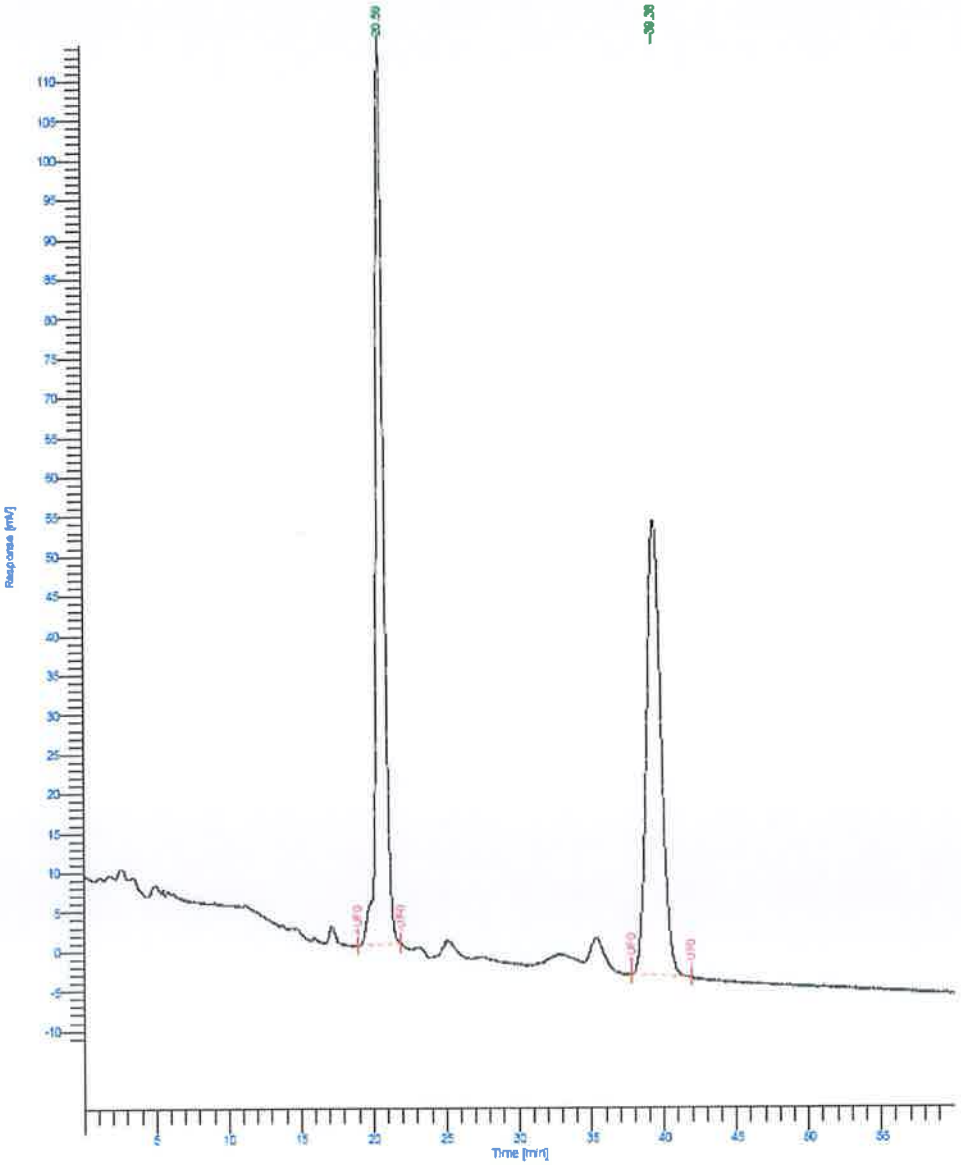
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		20.592	4218474.93	113617.98	51.41	51.41			*MM	4.2185	4.2185
2		39.380	3987866.24	57476.40	48.59	48.59			*MM	3.9879	3.9879
			8206341.17	171094.38	100.00	100.00				8.2063	8.2063

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20j

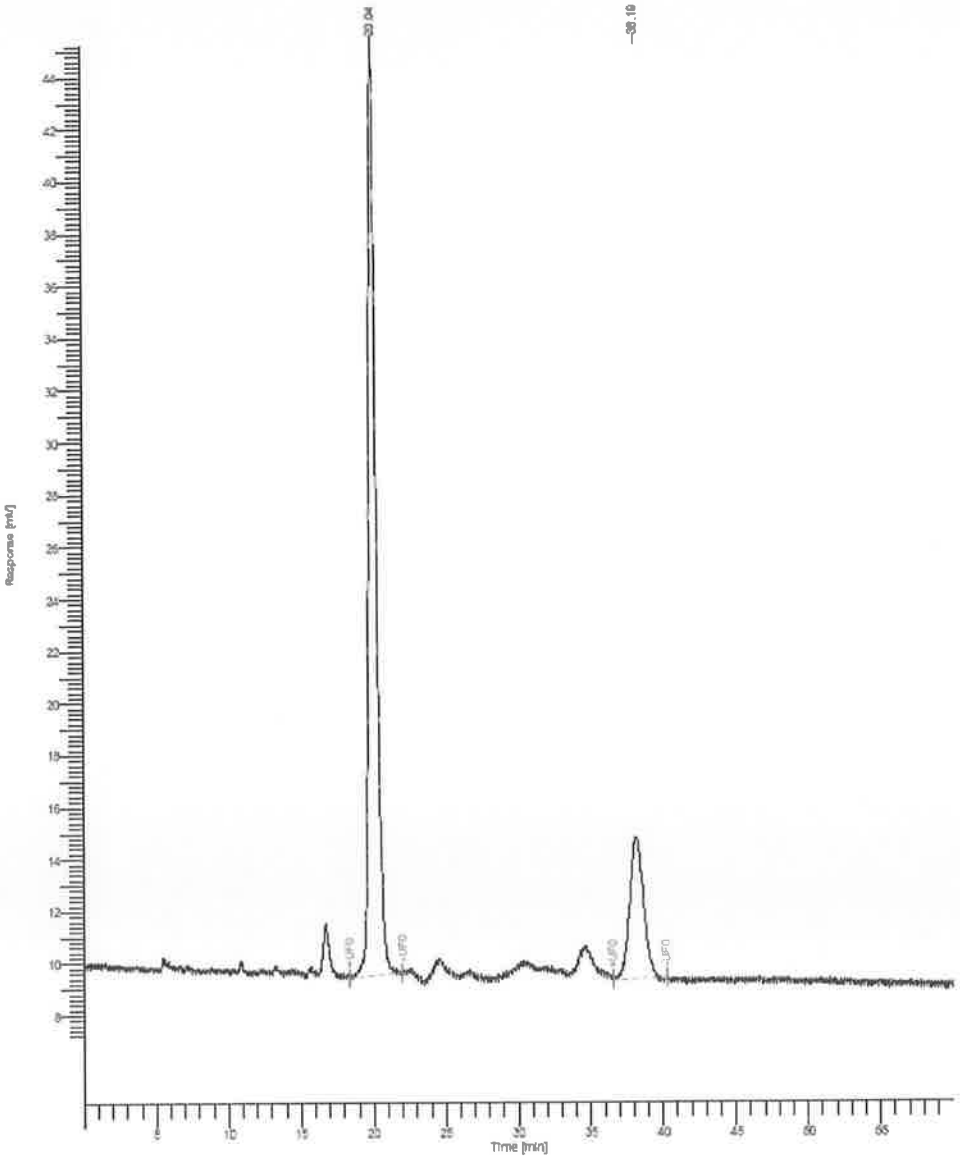
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		20.042	1298499.27	35711.29	78.07	78.07			*MM	1.2985	1.2985
2		38.192	364702.58	5443.93	21.93	21.93			*MM	0.3647	0.3647
			1663201.85	41155.22	100.00	100.00				1.6632	1.6632

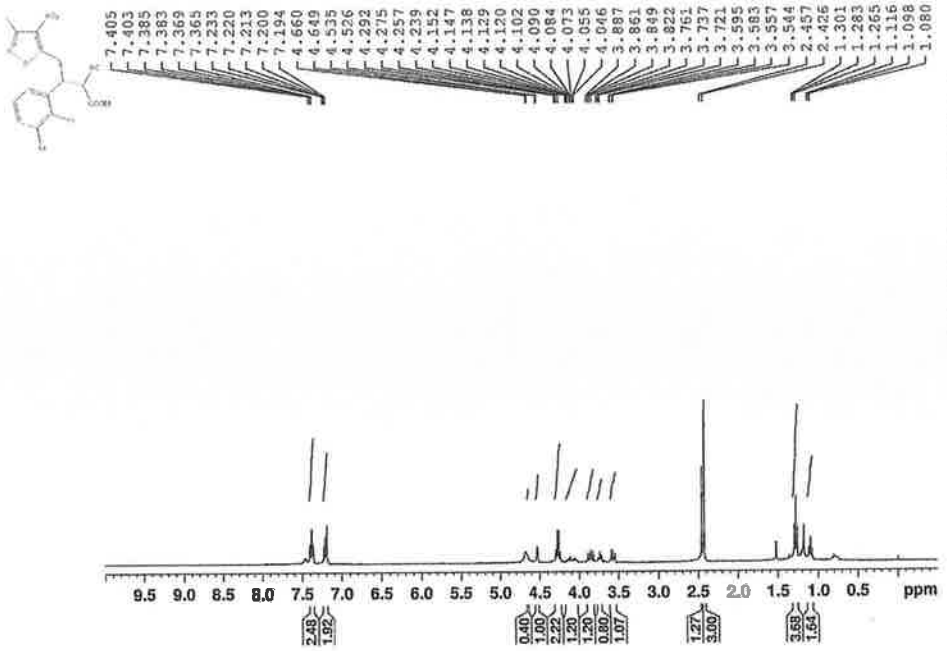
Missing Component Report

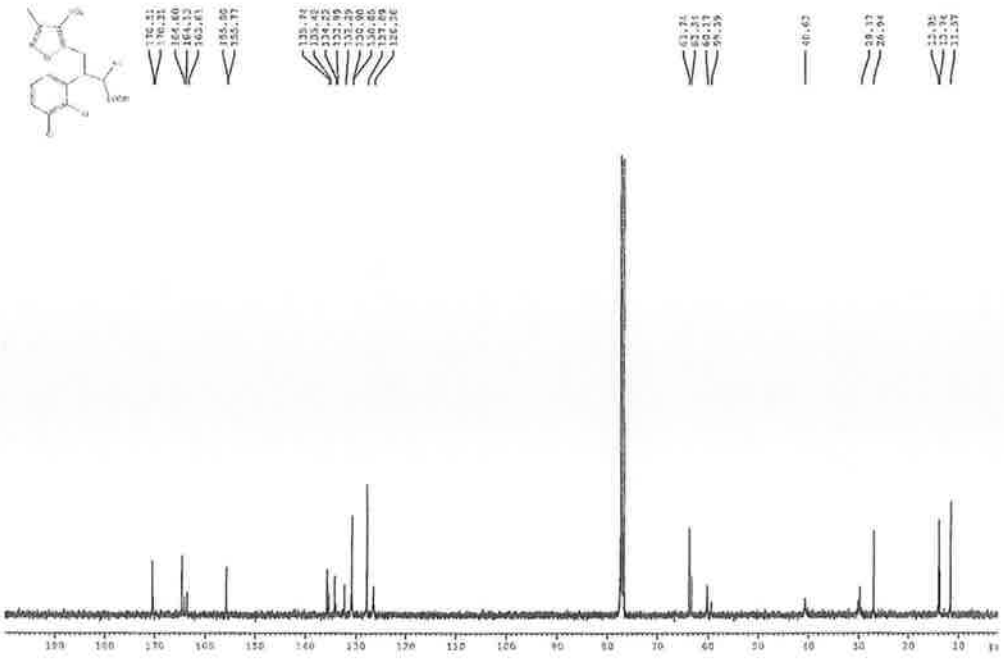
Component	Expected Retention (Calibration File)

All components were found

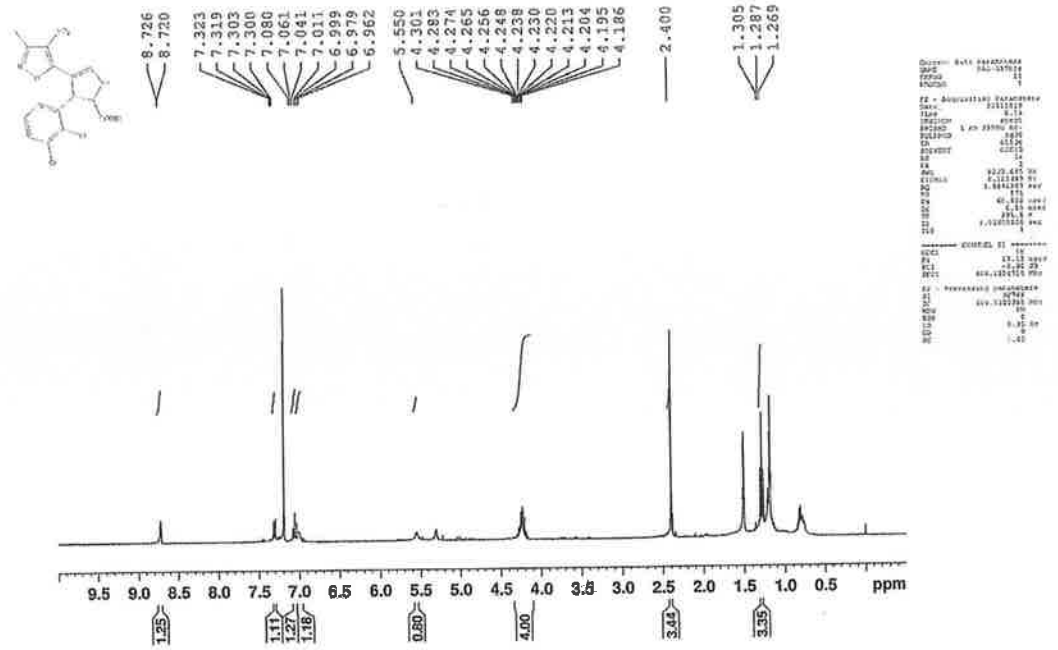


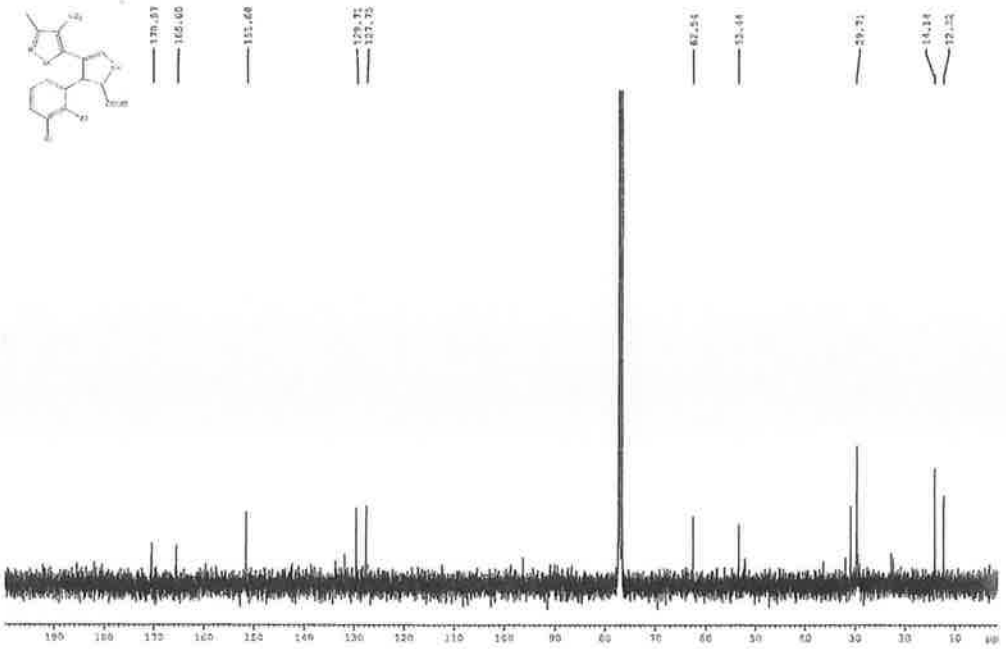
Compound 2.19k





Compound 2.20k





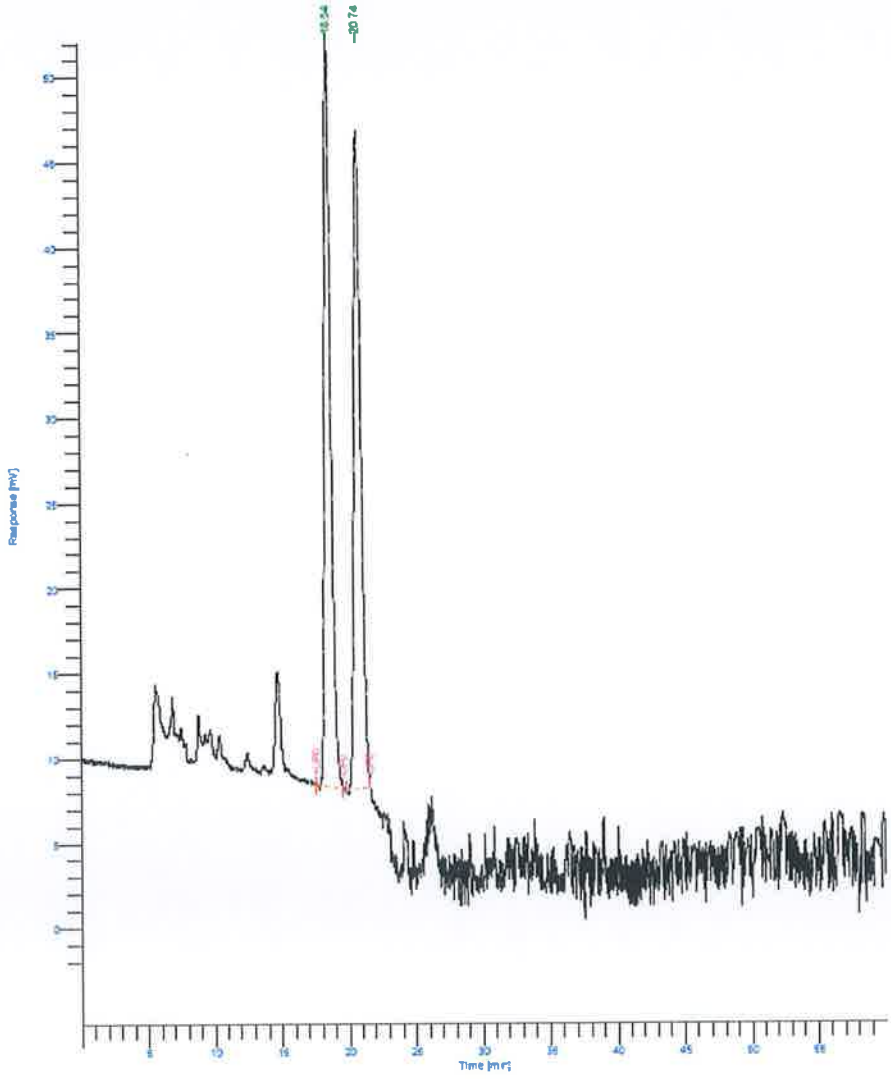
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.539	1430627.11	43764.08	50.59	50.59			*MM	1.4306	1.4306
2		20.739	1397103.17	38675.48	49.41	49.41			*MM	1.3971	1.3971
			2827730.27	82439.56	100.00	100.00				2.8277	2.8277

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20k

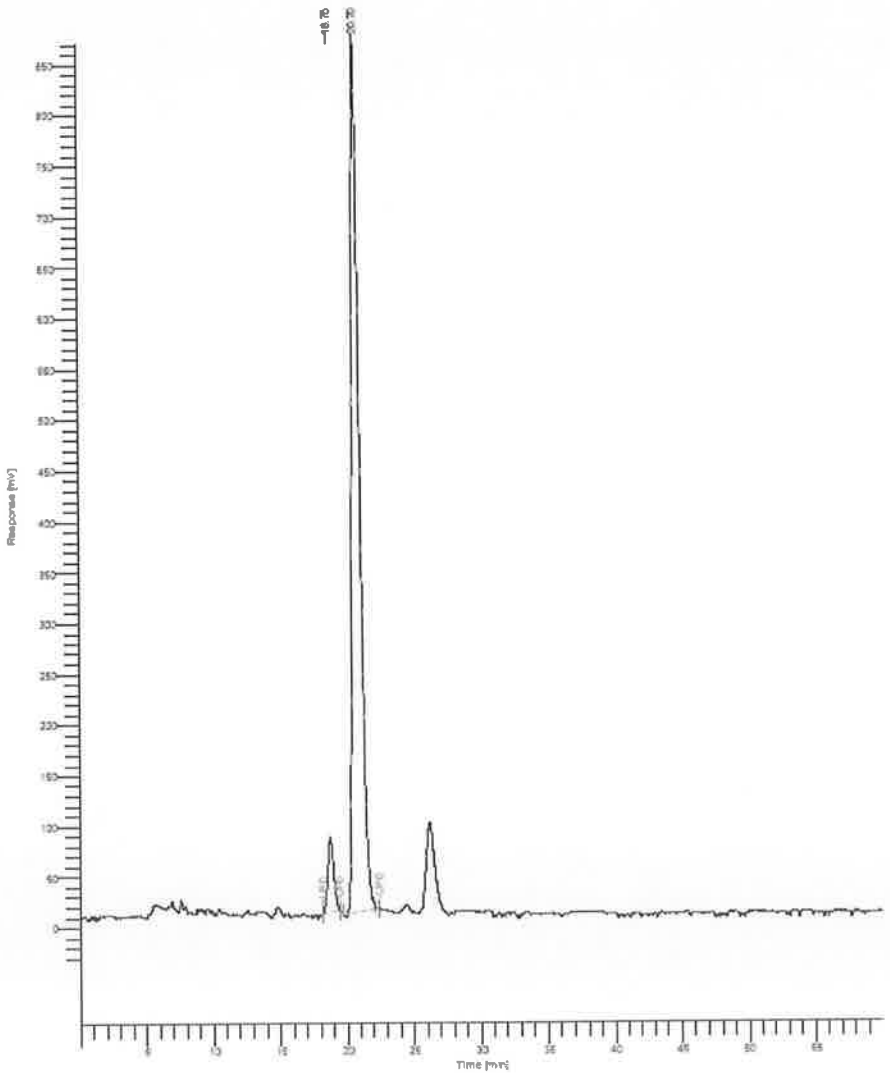
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		18.751	2301634.58	74000.52	6.22	6.22			*MM	2.3016	2.3016
2		20.702	34672464.36	856521.29	93.78	93.78			*MM	34.6725	34.6725
			36974098.94	930521.80	100.00	100.00				36.9741	36.9741

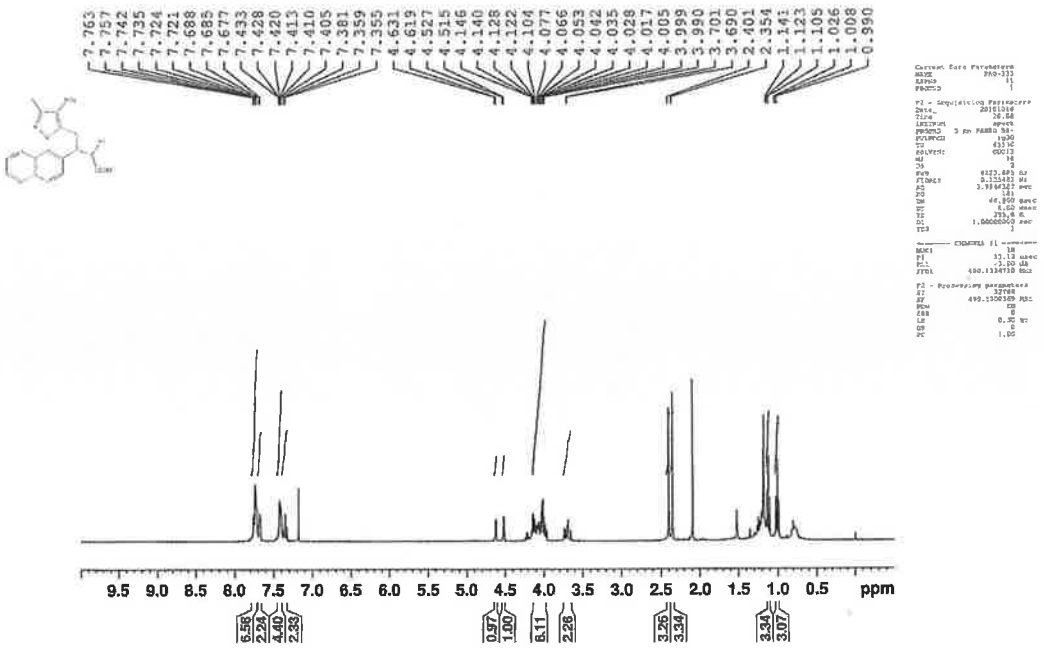
Missing Component Report

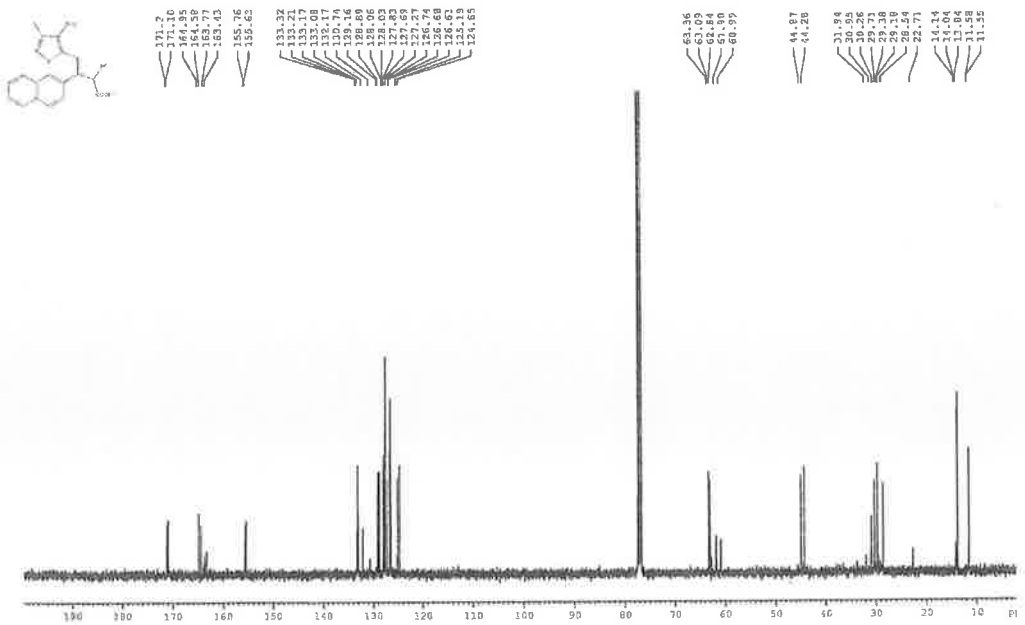
Component	Expected Retention (Calibration File)

All components were found

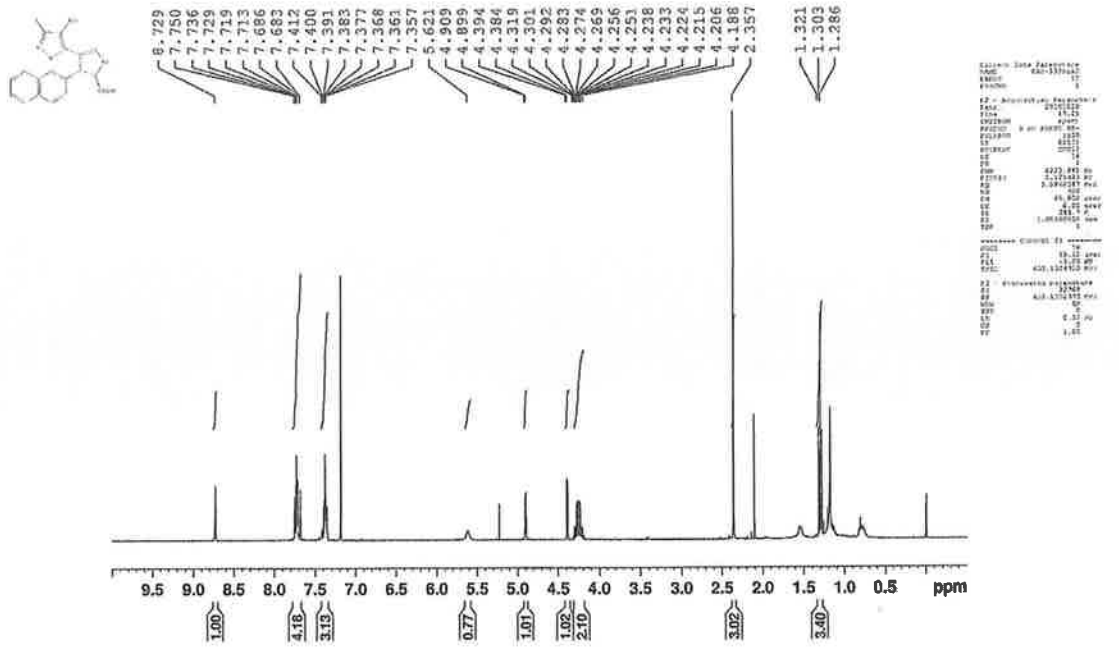


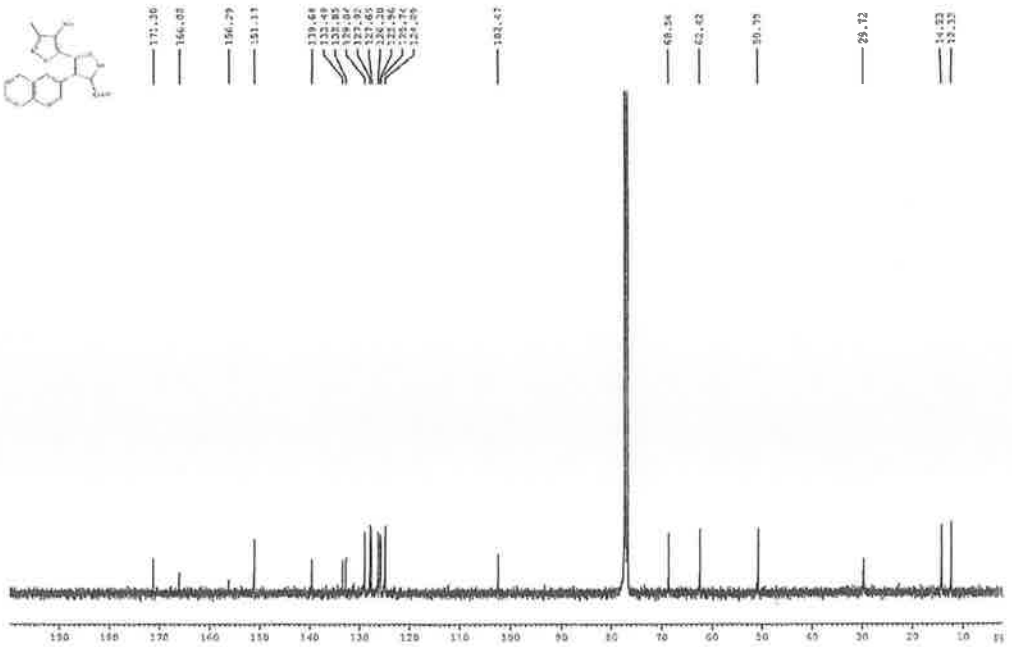
Compound 2.19l





Compound 2.20l



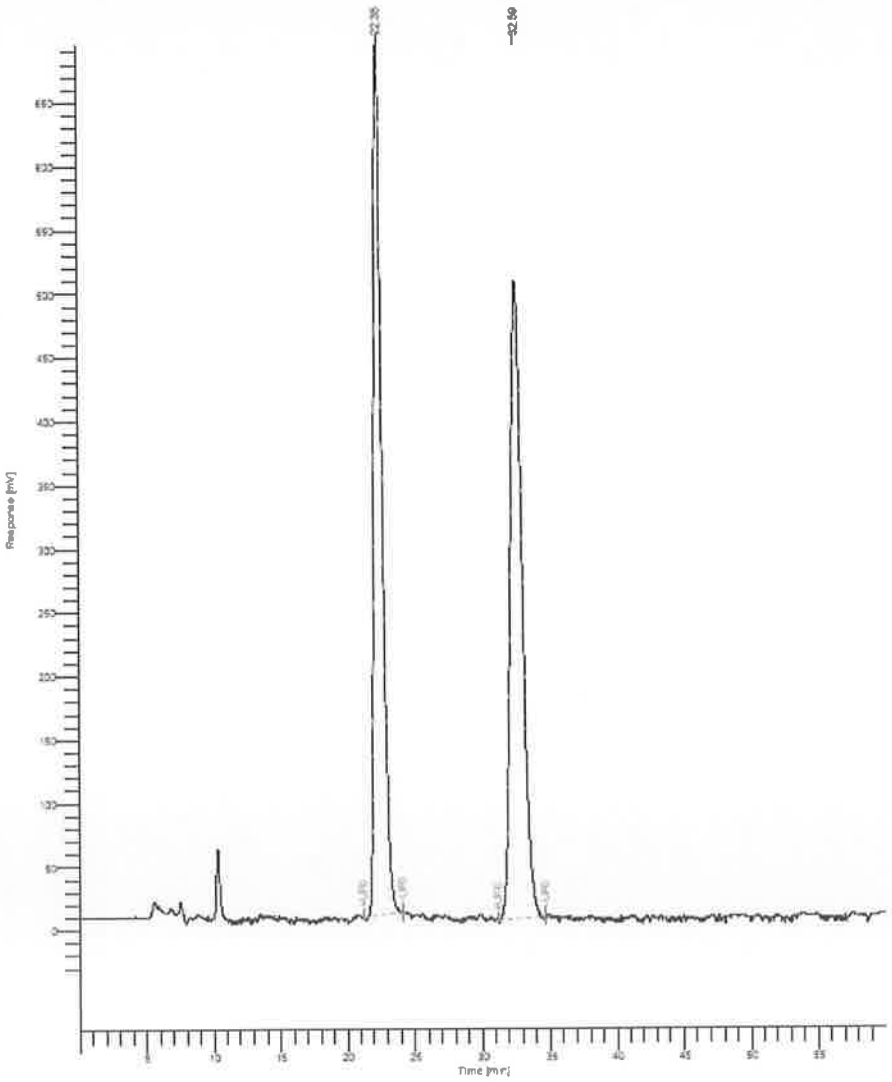


DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		22.352	29048951.17	684614.50	49.48	49.48			*MM	29.0490	29.0490
2		32.589	29664832.13	500481.09	50.52	50.52			*MM	29.6648	29.6648
			58713783.30	1.19e+06	100.00	100.00				58.7138	58.7138

Missing Component Report
Component Expected Retention (Calibration File)

All components were found



Compound 2.20l

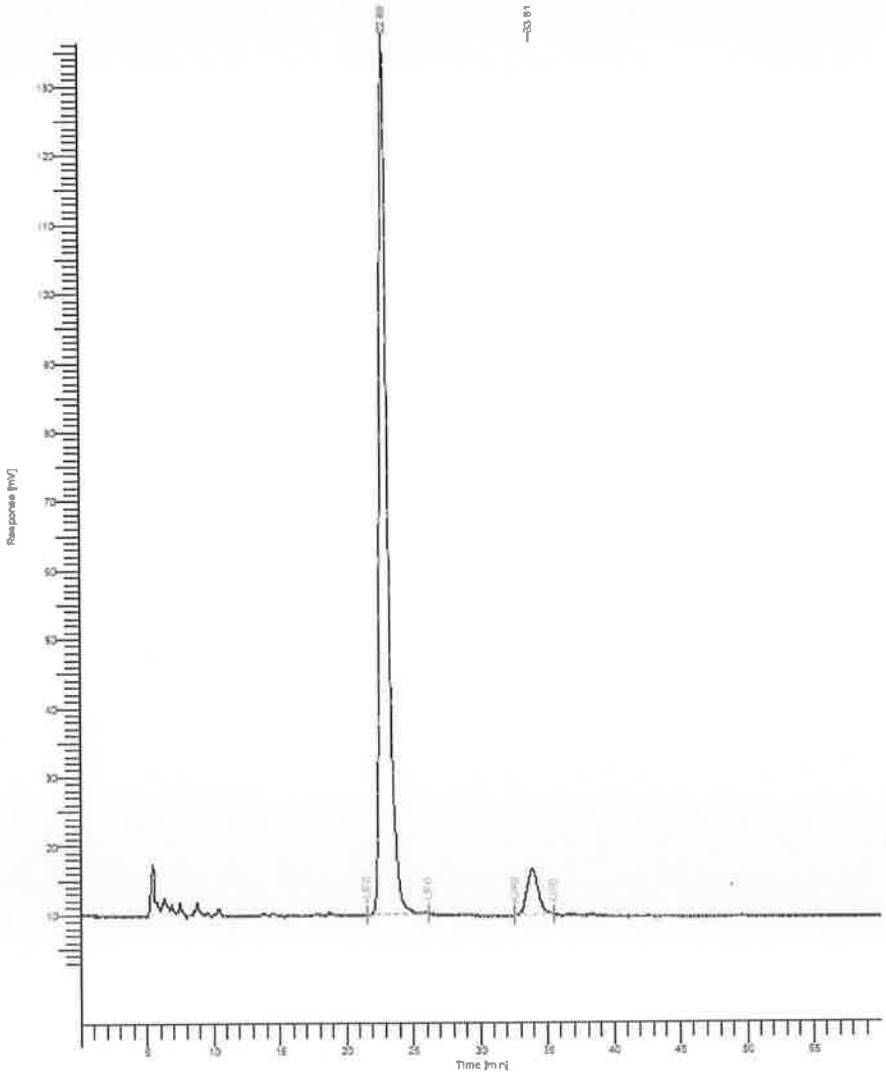
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		22.895	5504830.35	126372.33	93.23	93.23			*MM	5.5048	5.5048
2		33.807	399618.22	6647.49	6.77	6.77			*MM	0.3996	0.3996
			5904448.57	133019.82	100.00	100.00				5.9044	5.9044

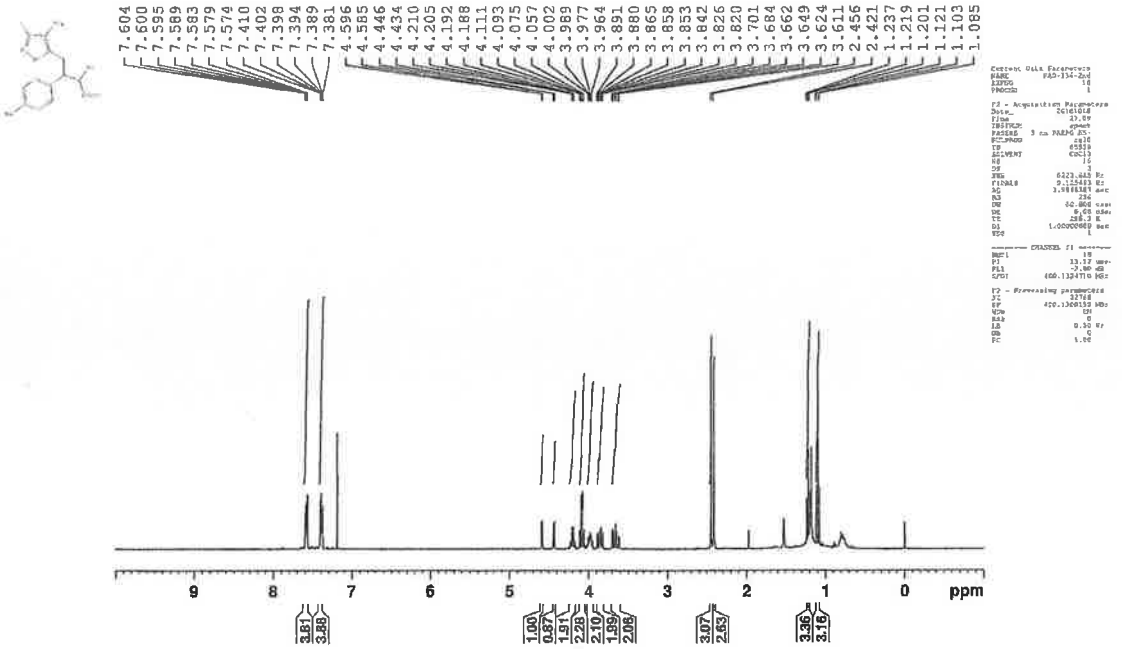
Missing Component Report

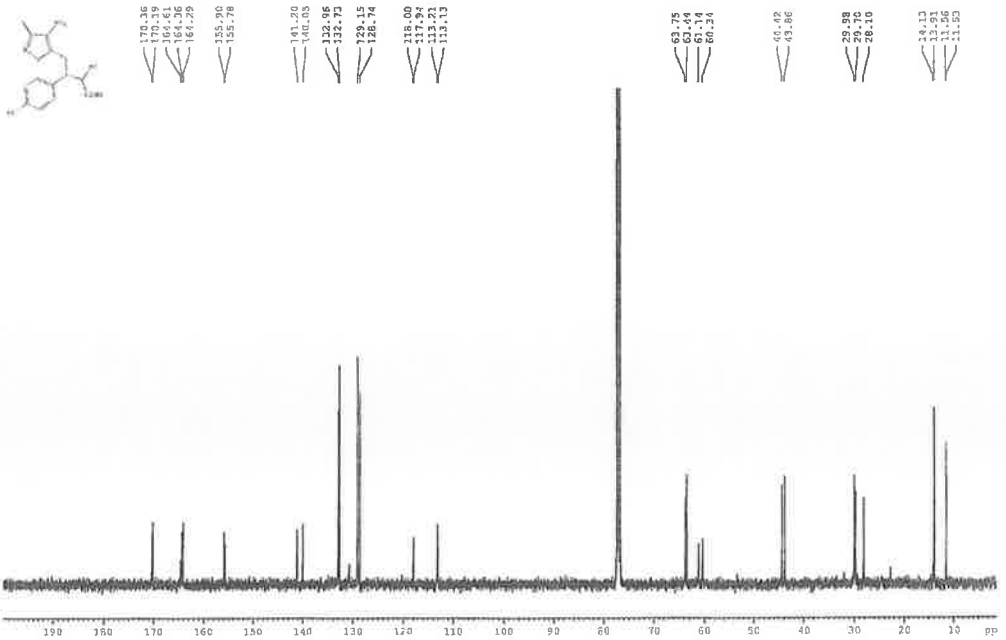
Component	Expected Retention (Calibration File)

All components were found

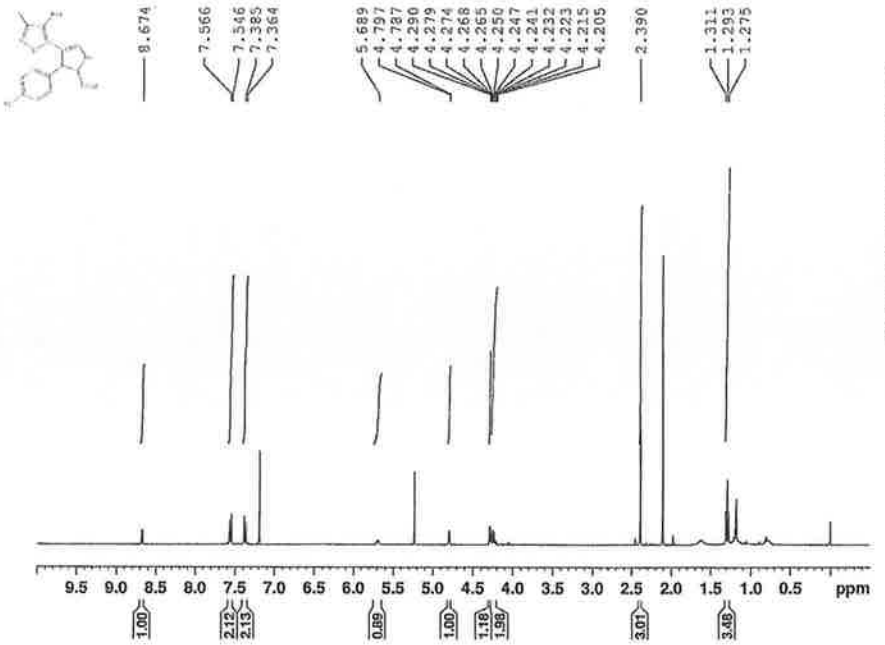


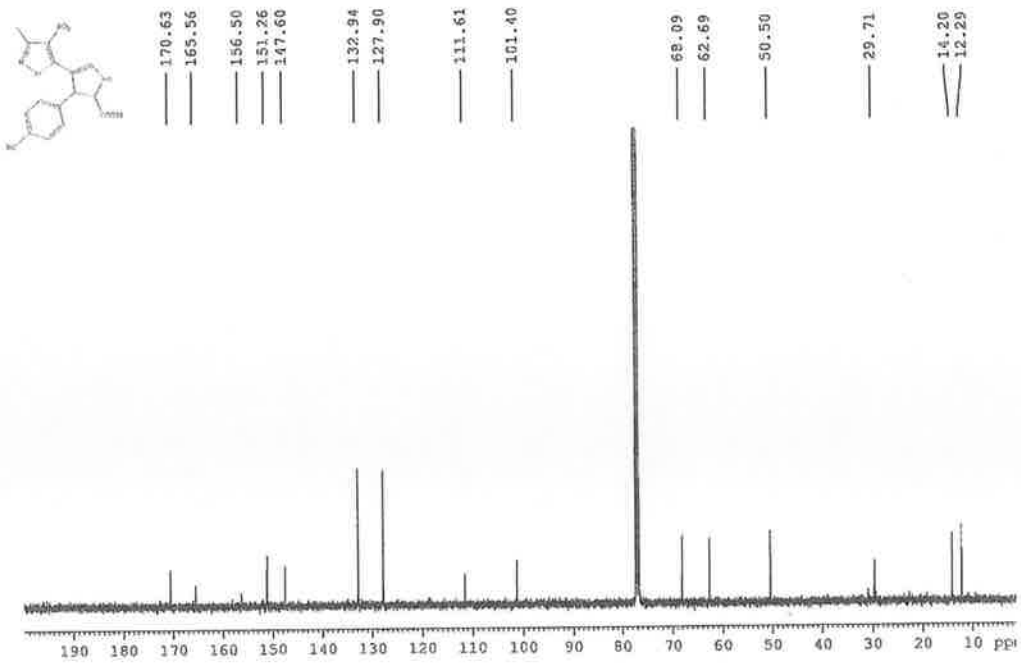
Compound 2.19m





Compound 2.20m





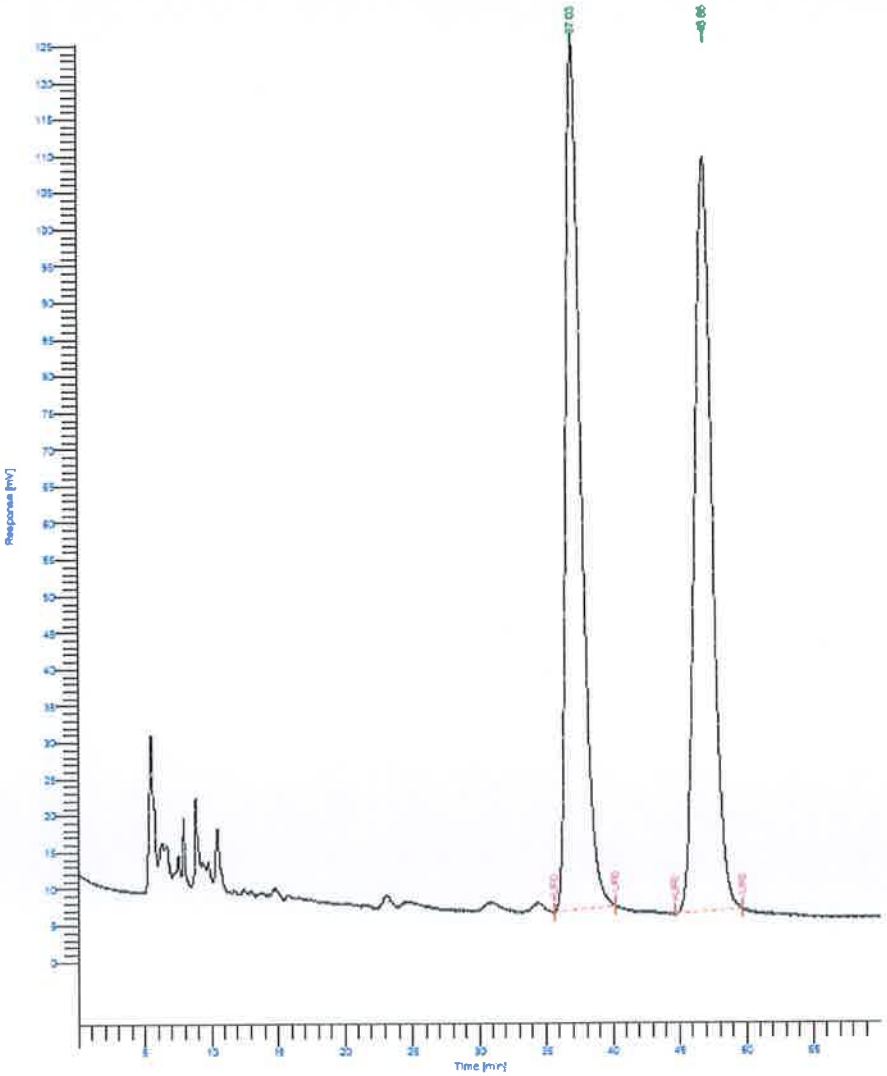
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		37.033	9320890.18	118329.75	50.03	50.03			*MM	9.3209	9.3209
2		46.845	9311256.89	102801.56	49.97	49.97			*MM	9.3113	9.3113
			18632147.07	221131.31	100.00	100.00				18.6321	18.6321

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.20m

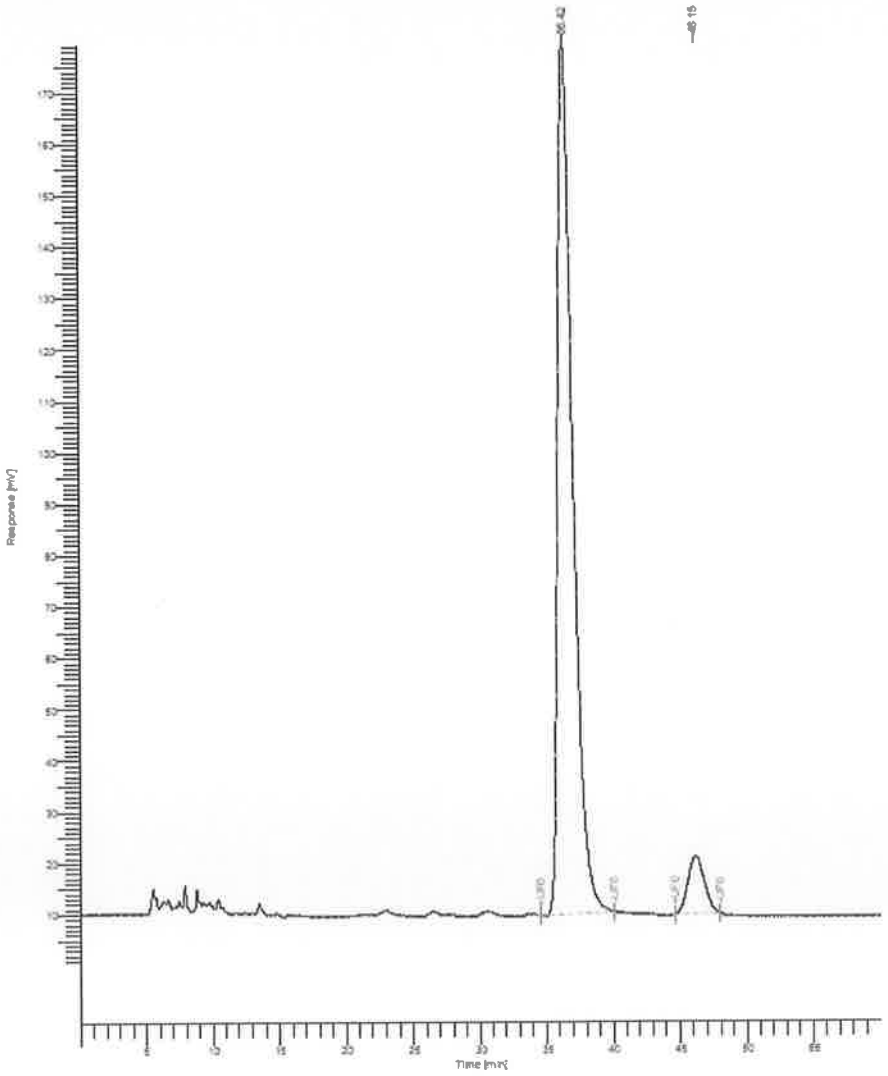
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		36.417	13374824.13	169807.58	93.35	93.35			*MM	13.3748	13.3748
2		46.149	952769.30	11303.15	6.65	6.65			*MM	0.9528	0.9528
			14327593.43	180910.73	100.00	100.00				14.3276	14.3276

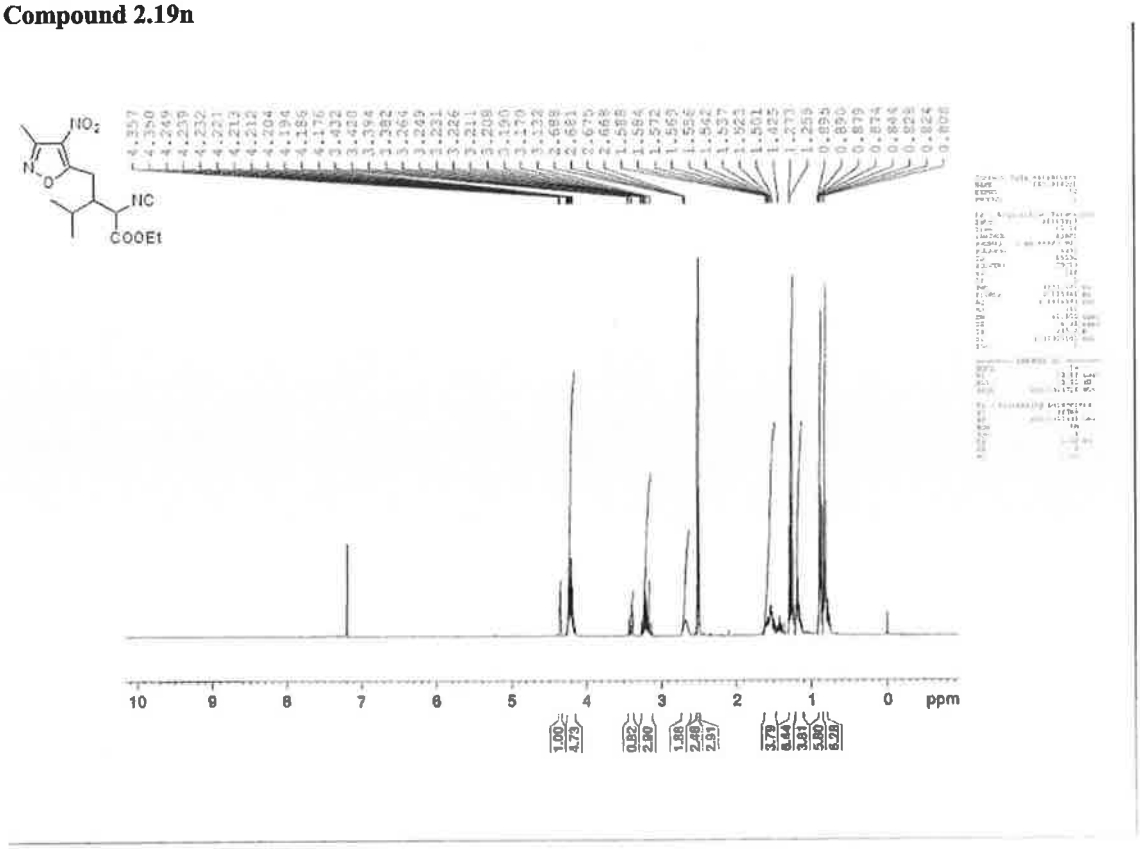
Missing Component Report

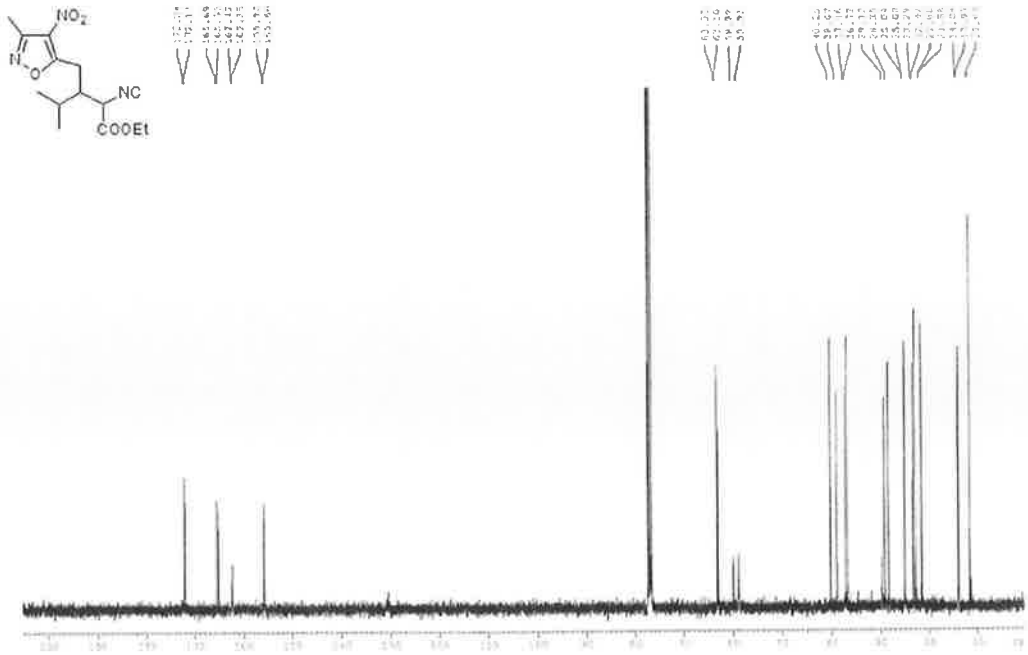
Component	Expected Retention (Calibration File)

All components were found

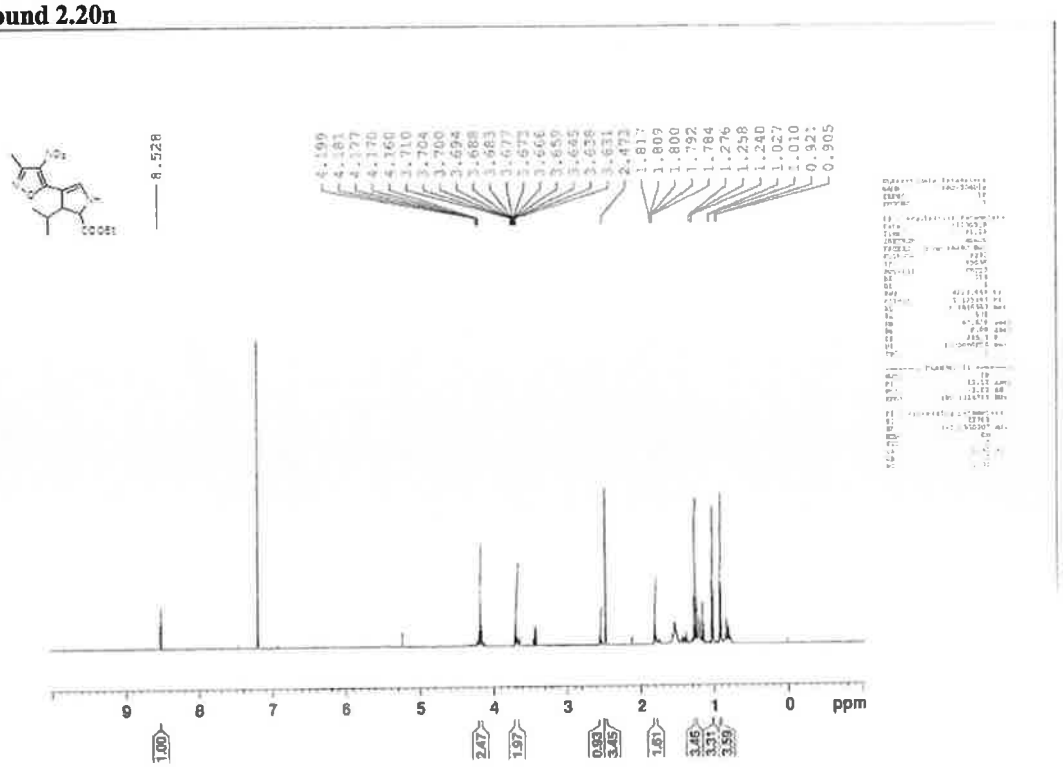


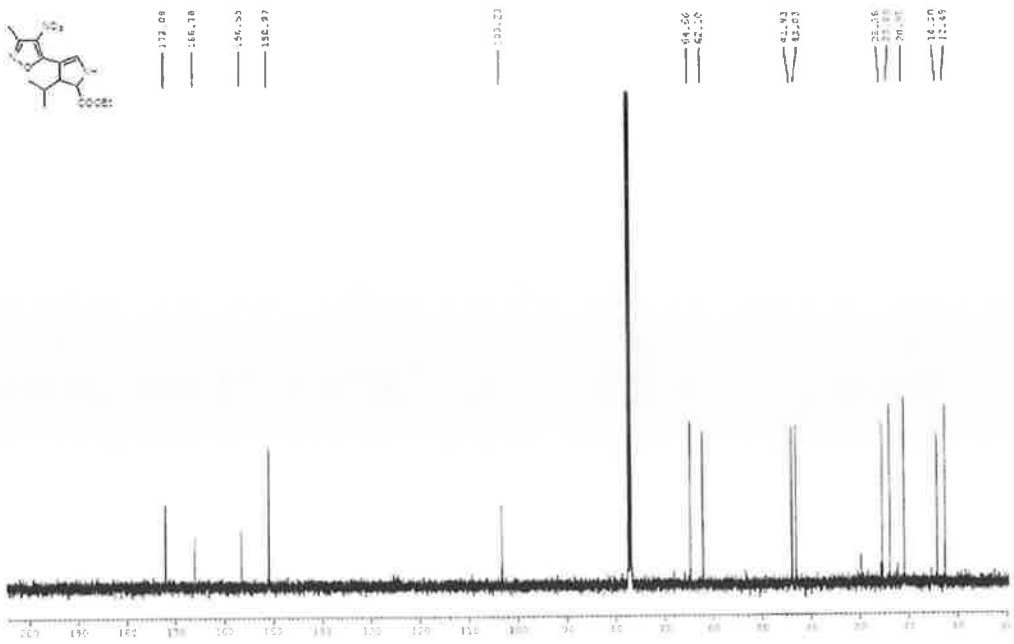
Compound 2.19n





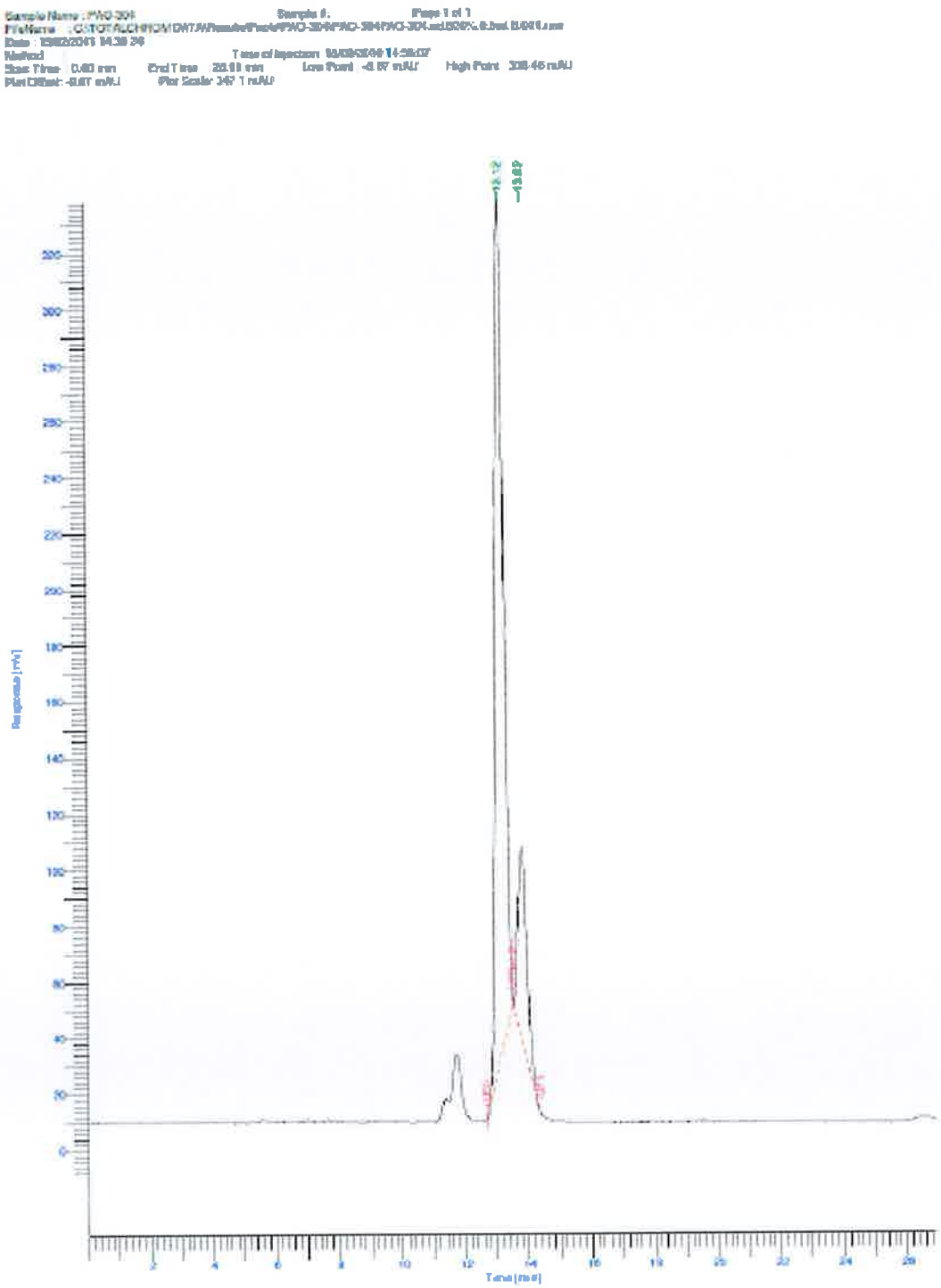
Compound 2.20n



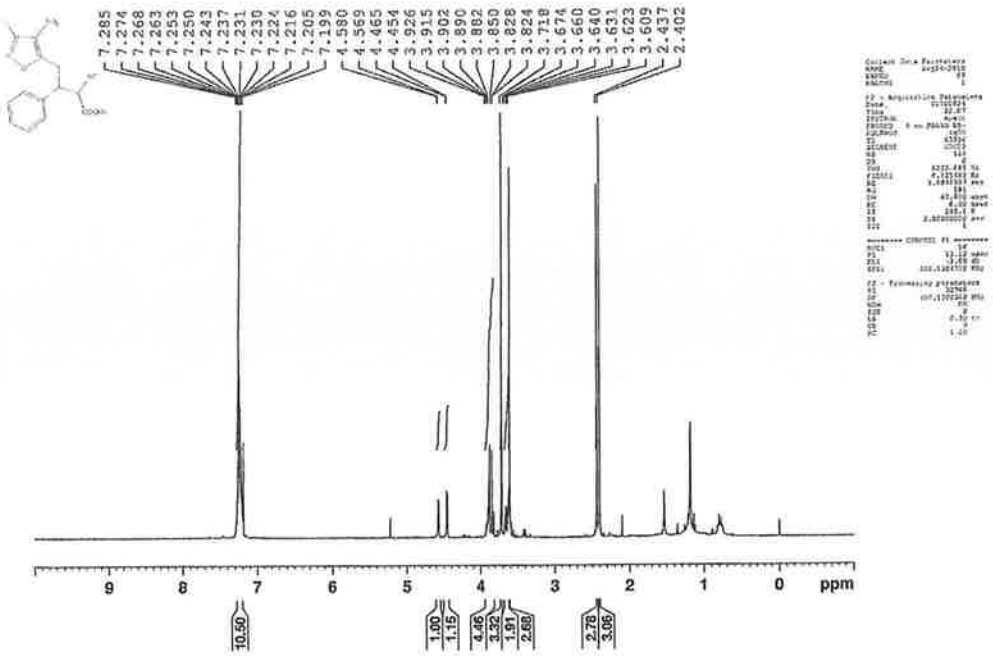


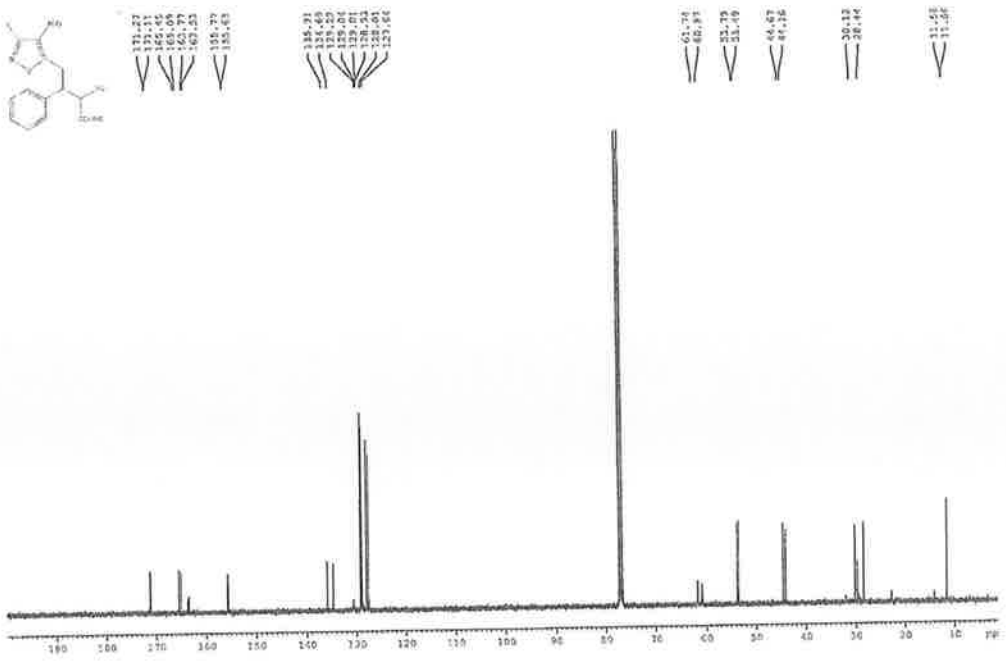
Compound 2.20n

Compound 2.20n

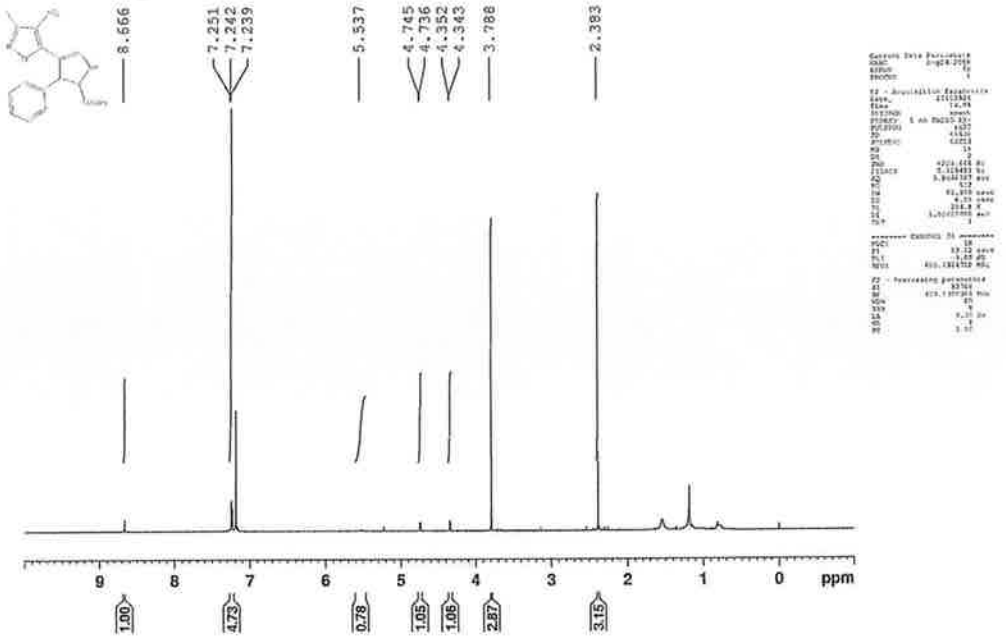


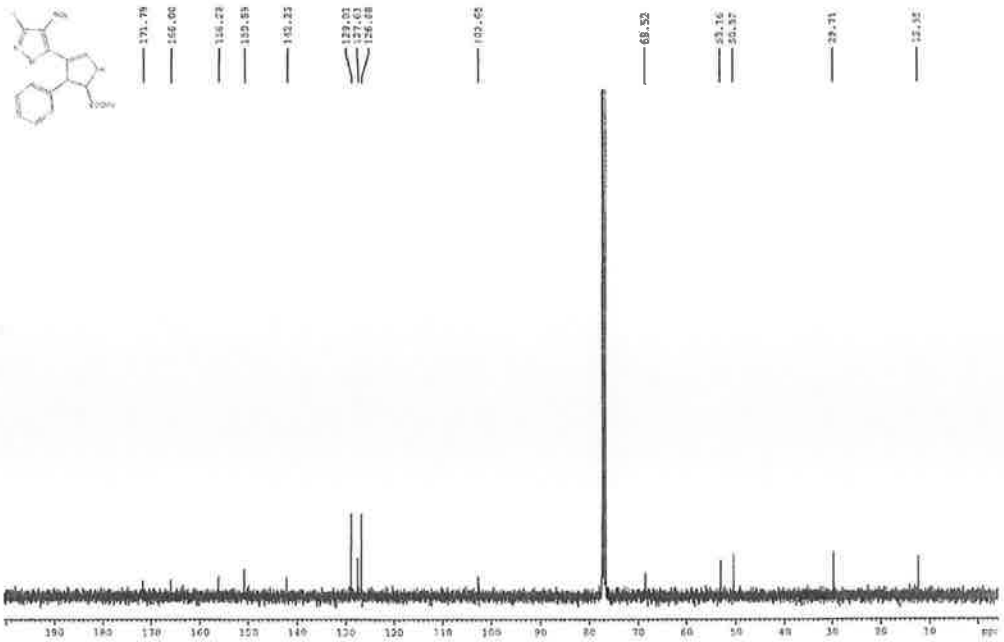
Compound 2.41a





Compound 2.42a





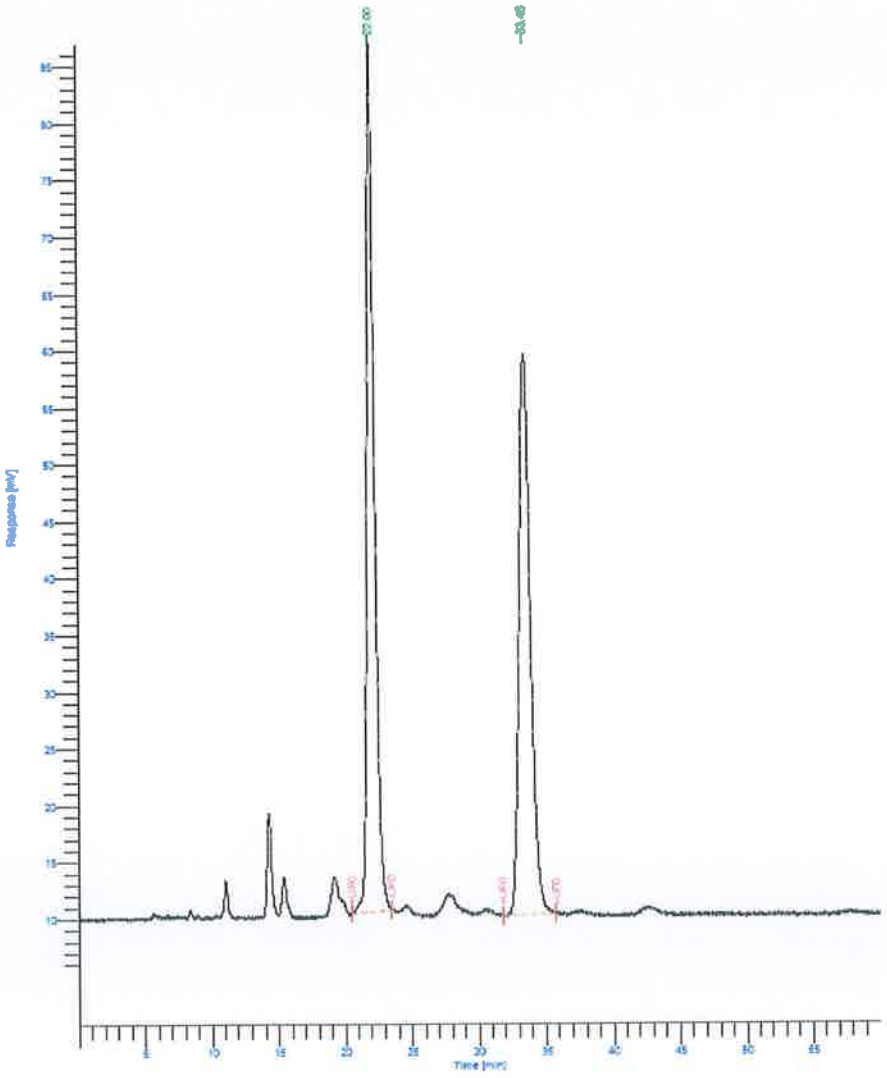
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		22.080	3040136.96	76411.87	51.38	51.38			*MM	3.0401	3.0401
2		33.462	2877081.63	49289.75	48.62	48.62			*MM	2.8771	2.8771
			5917217.59	125701.61	100.00	100.00				5.9172	5.9172

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.42a

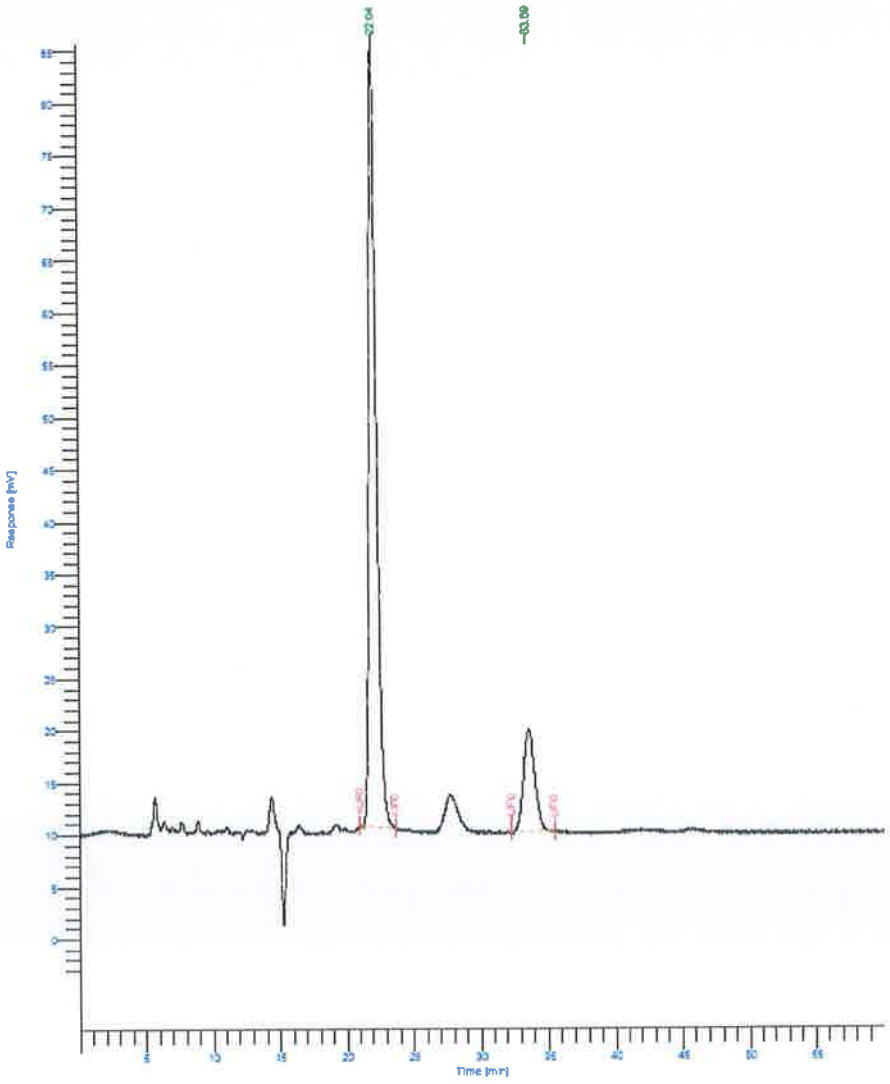
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		22.037	2900513.45	75010.82	83.66	83.66			*MM	2.9005	2.9005
2		33.587	566387.15	9874.12	16.34	16.34			*MM	0.5664	0.5664
			3466900.60	84884.94	100.00	100.00				3.4669	3.4669

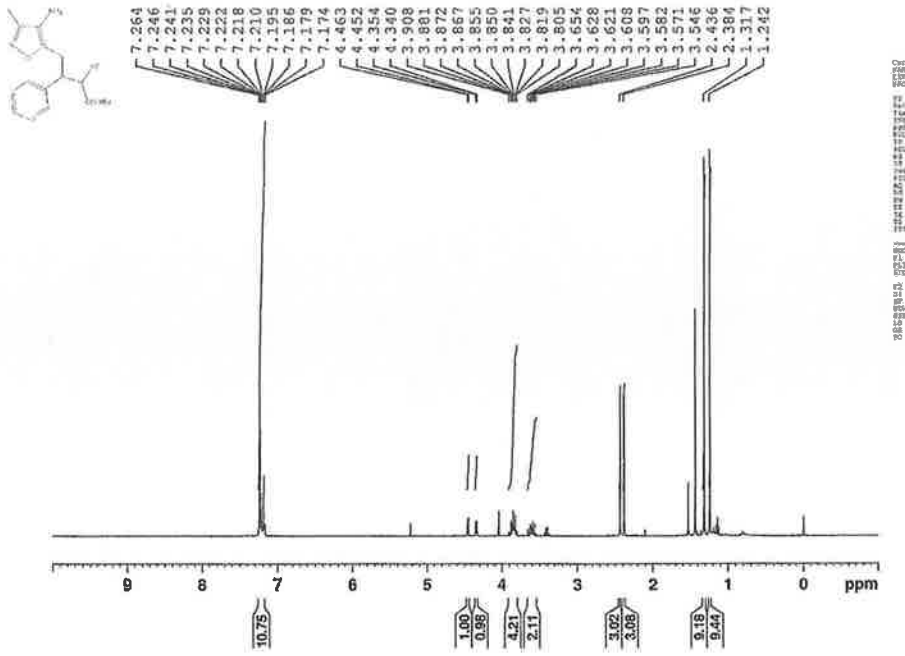
Missing Component Report

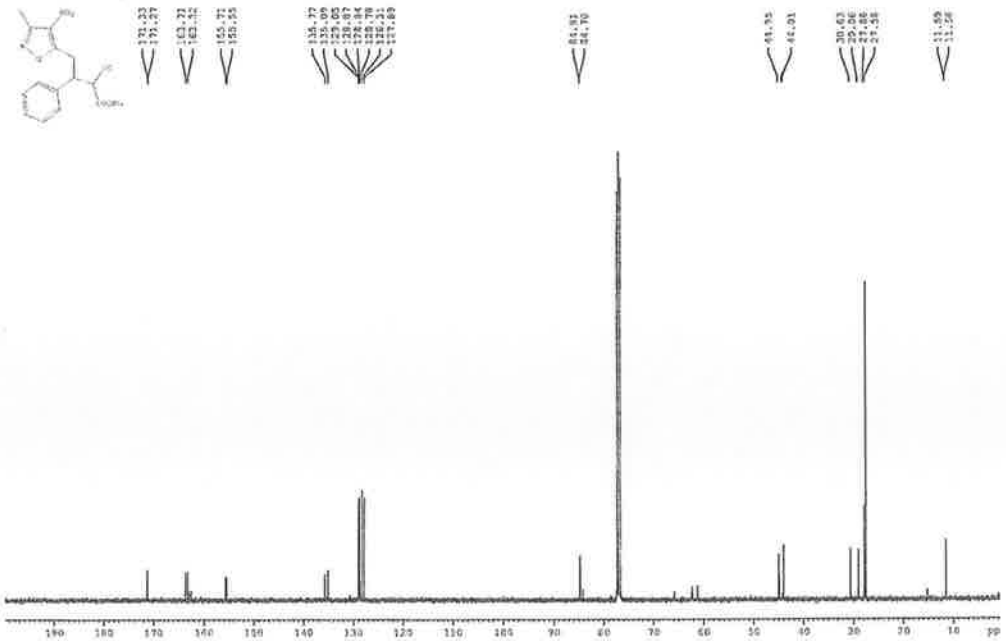
Component	Expected Retention (Calibration File)

All components were found

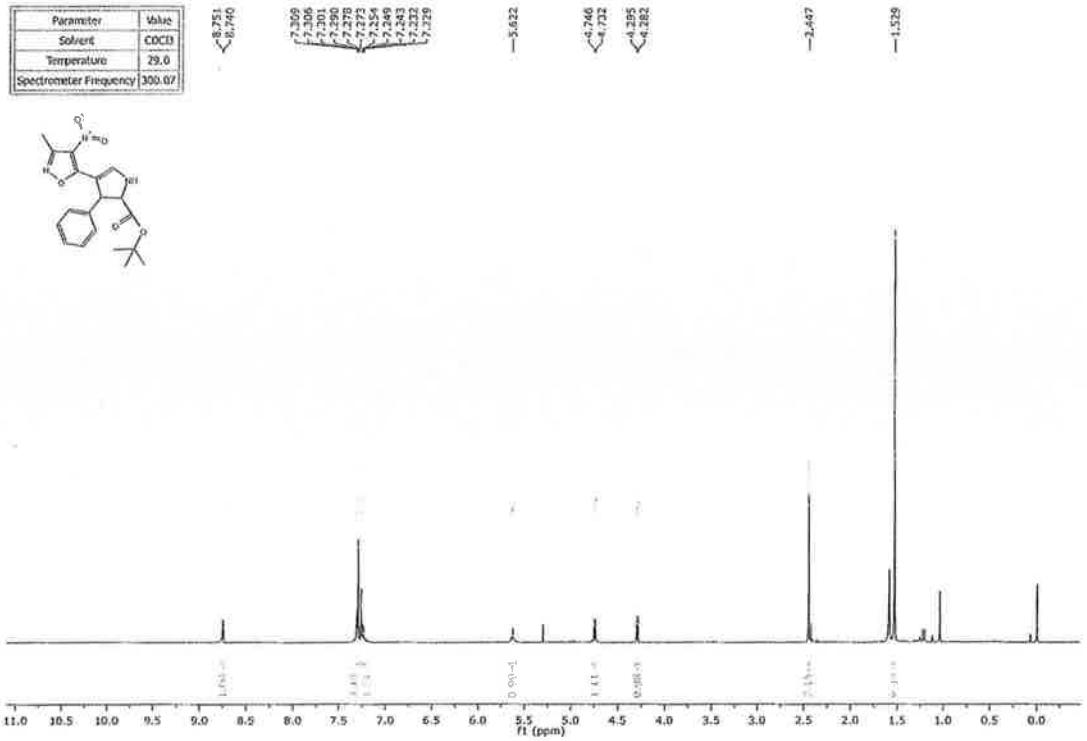


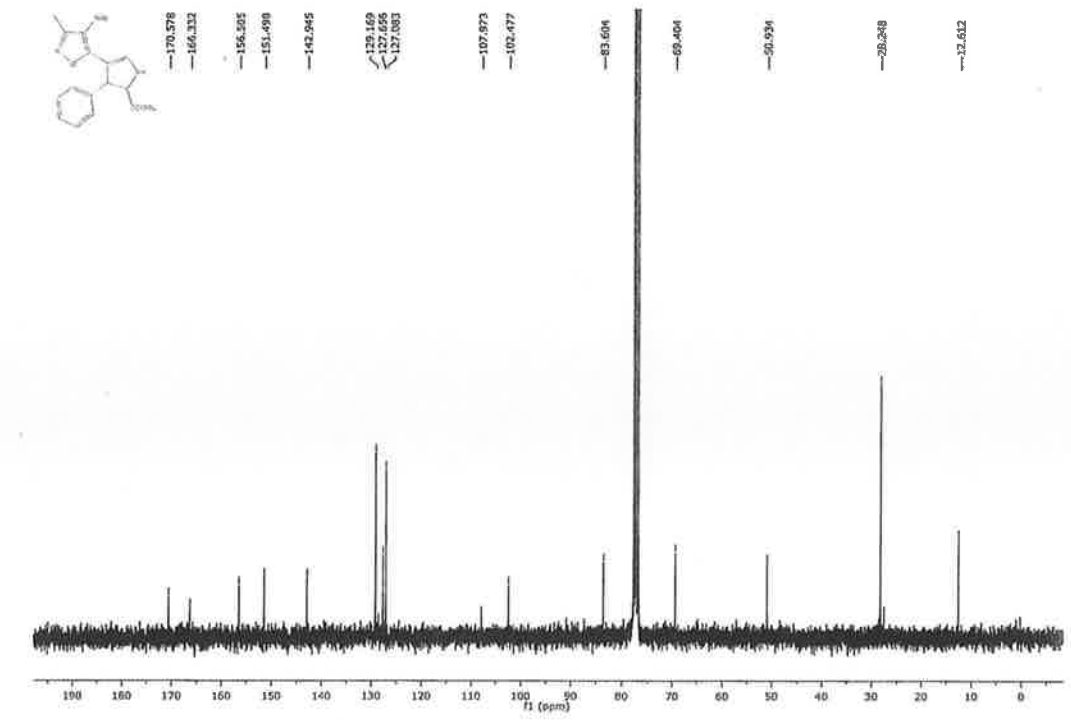
Compound 2.41b





Compound 2.42b





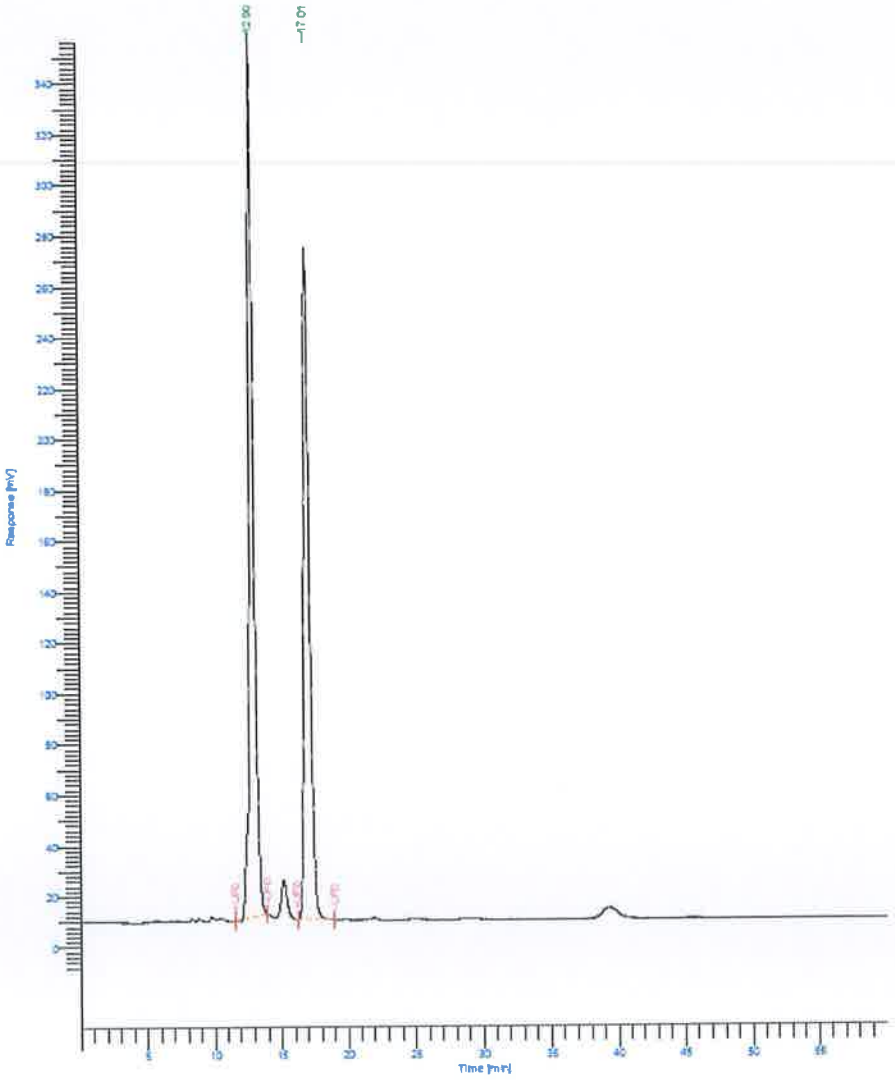
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		12.899	9037317.39	344505.54	53.58	53.58			*MM	9.0373	9.0373
2		17.006	7830869.57	264075.47	46.42	46.42			*MM	7.8309	7.8309
			16868186.97	608581.02	100.00	100.00				16.8682	16.8682

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Compound 2.42b

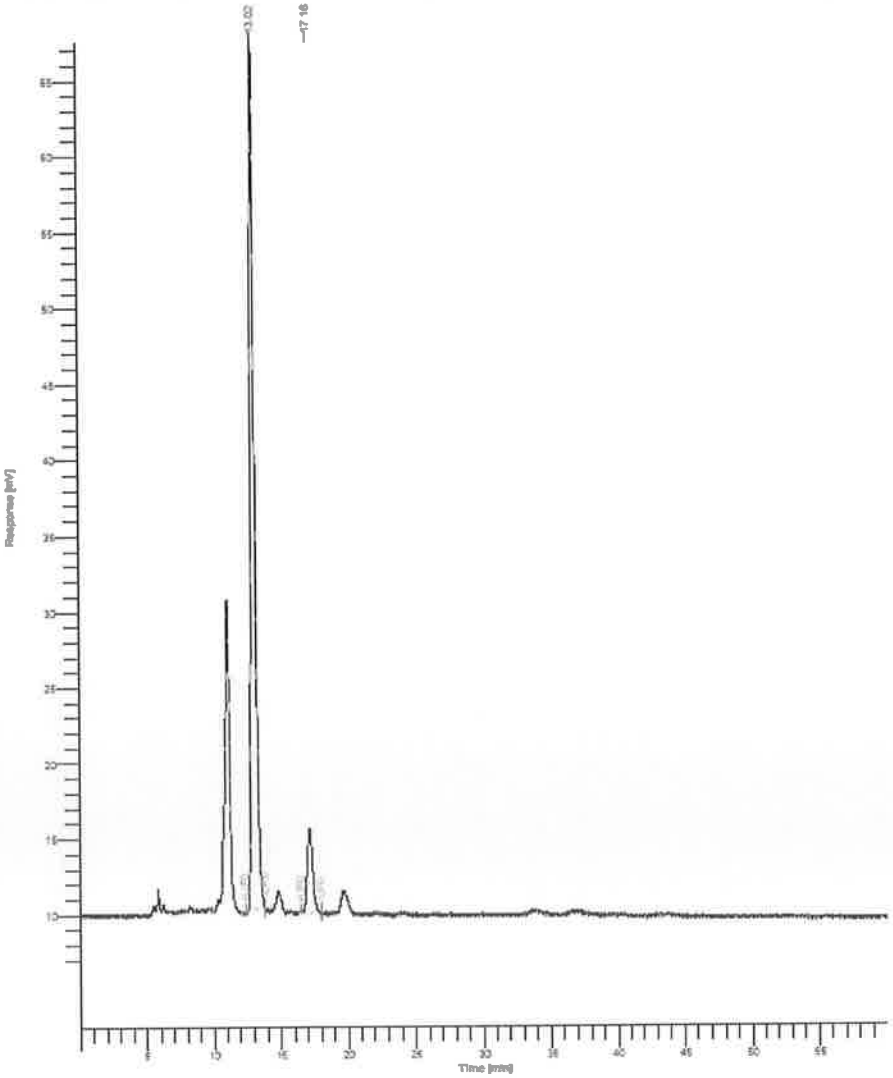
DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Cal. Range	Volt Range	BL	Raw Amount	Adjusted Amount
1		13.017	1229804.42	57243.65	88.67	88.67			*MM	1.2298	1.2298
2		17.160	157067.48	5547.02	11.33	11.33			*MM	0.1571	0.1571
			1386871.90	62790.67	100.00	100.00				1.3869	1.3869

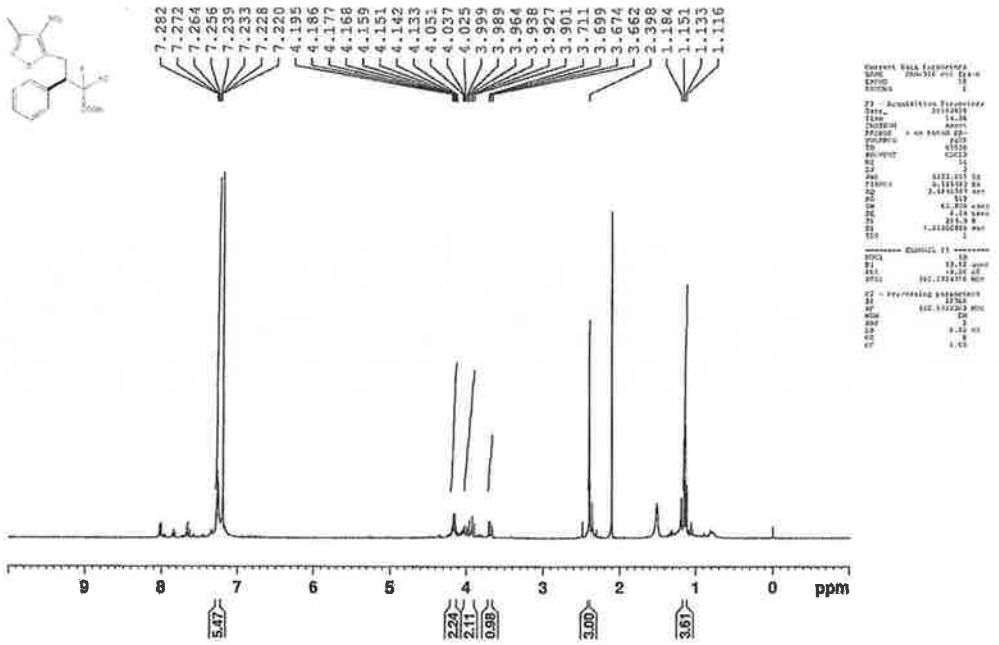
Missing Component Report

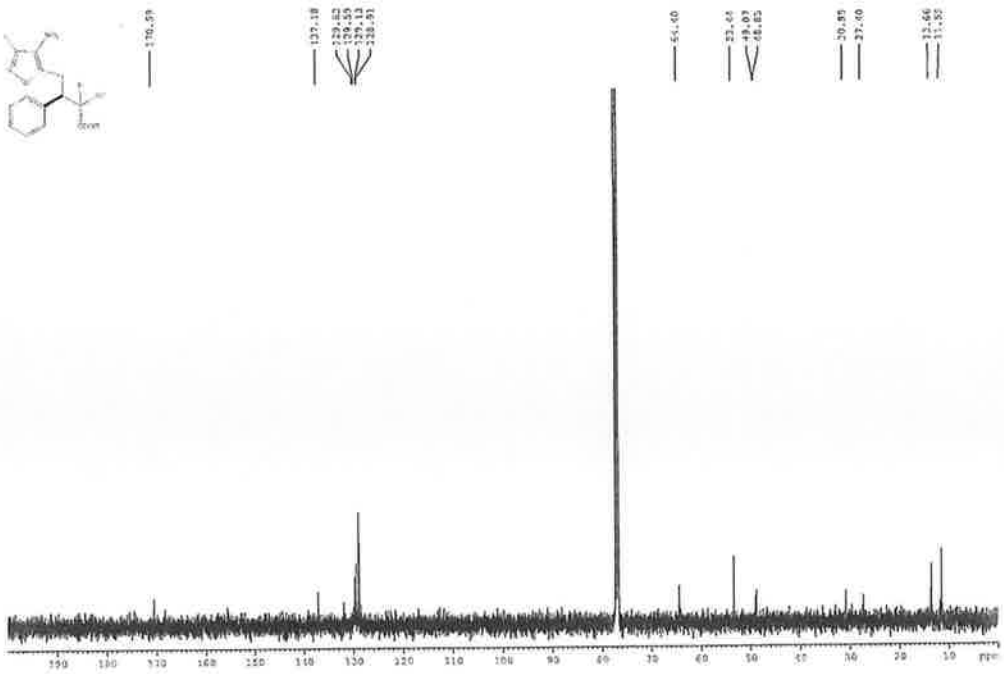
Component	Expected Retention (Calibration File)

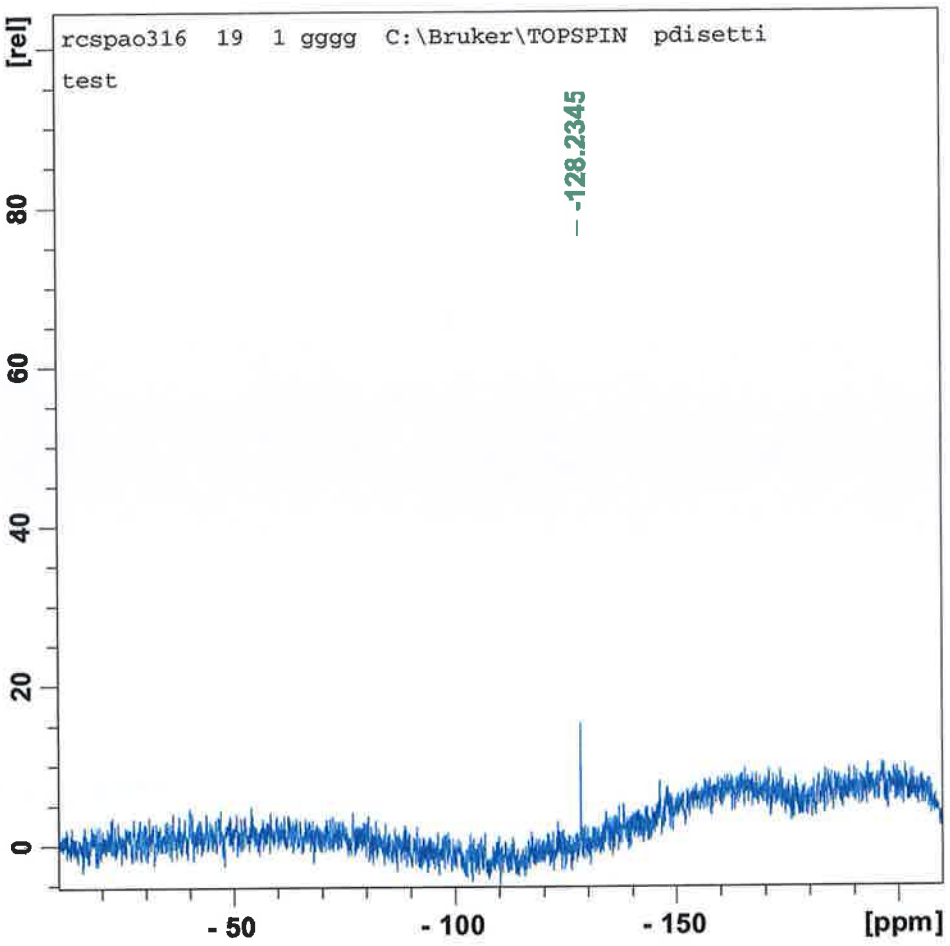
All components were found



Compound 2.43



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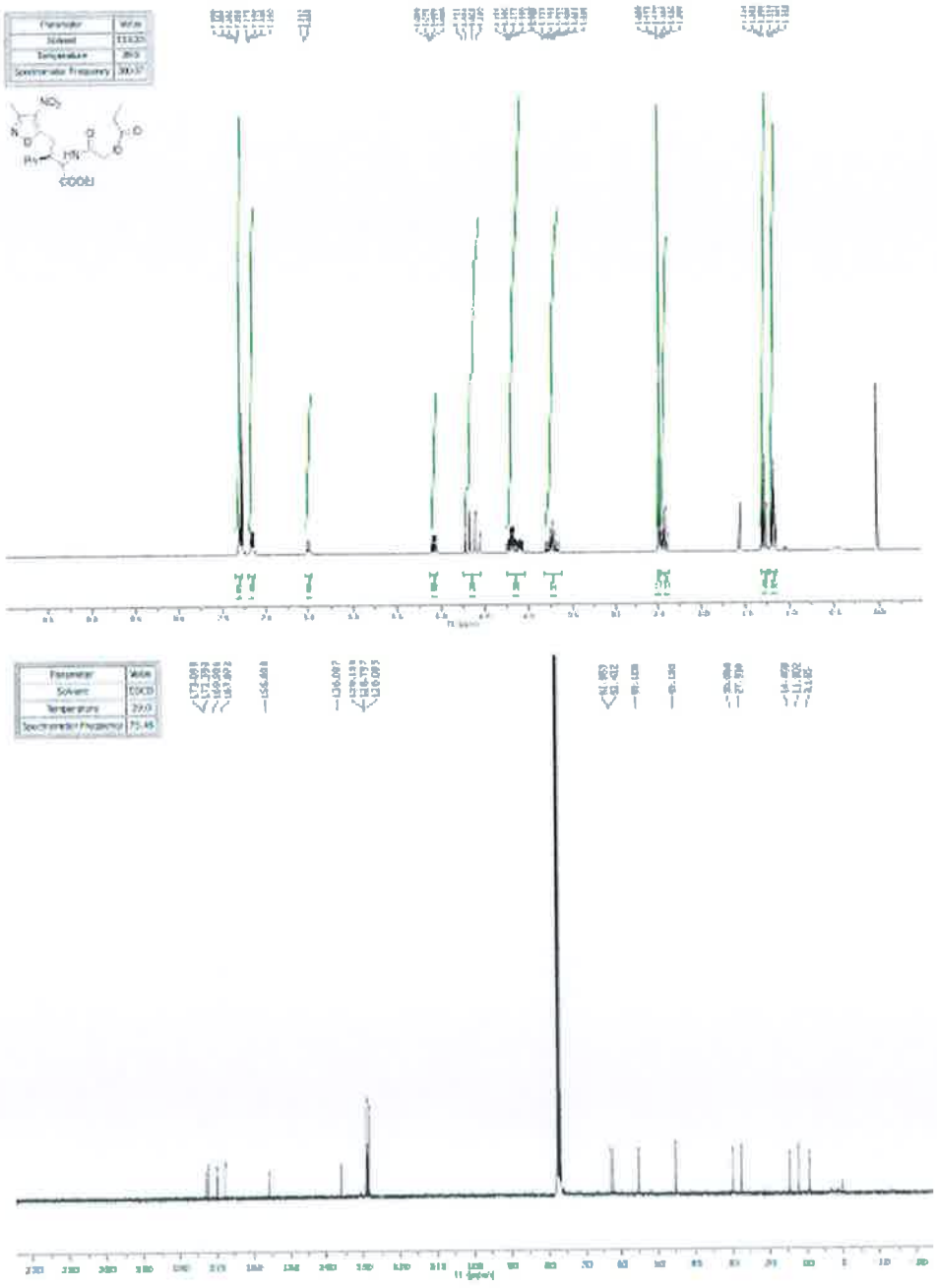
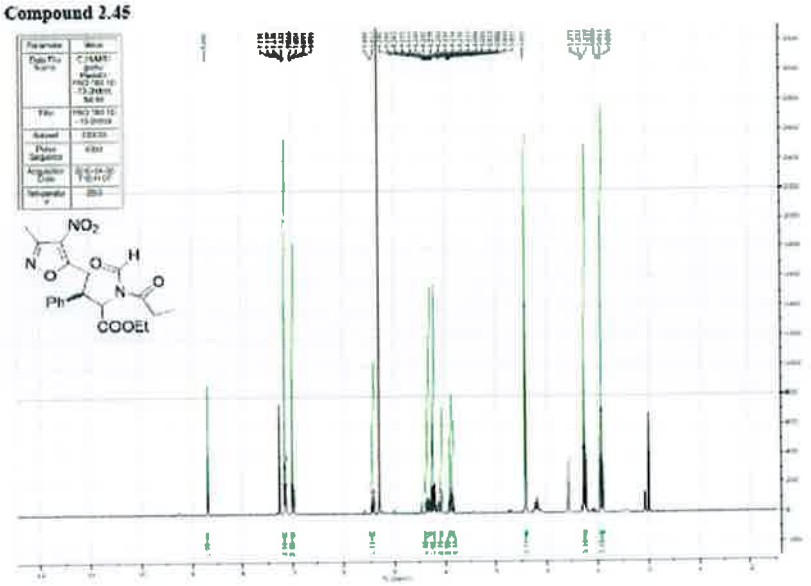
80
- 50
- 100
- 150
[ppm]

Compound 2.44

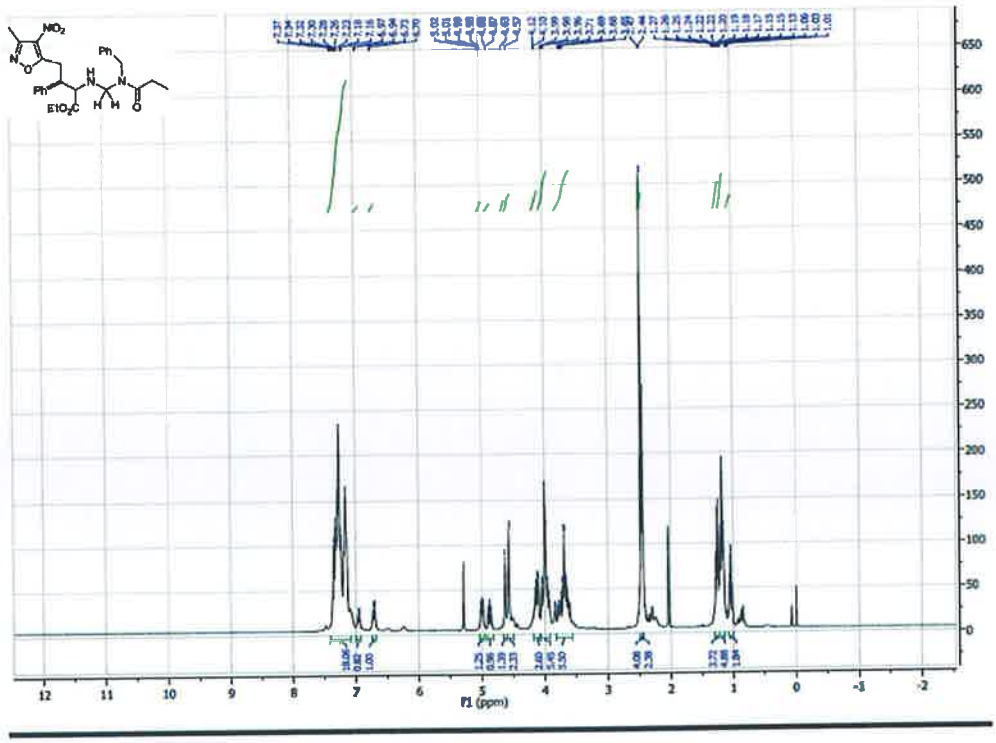
Compound 2.44



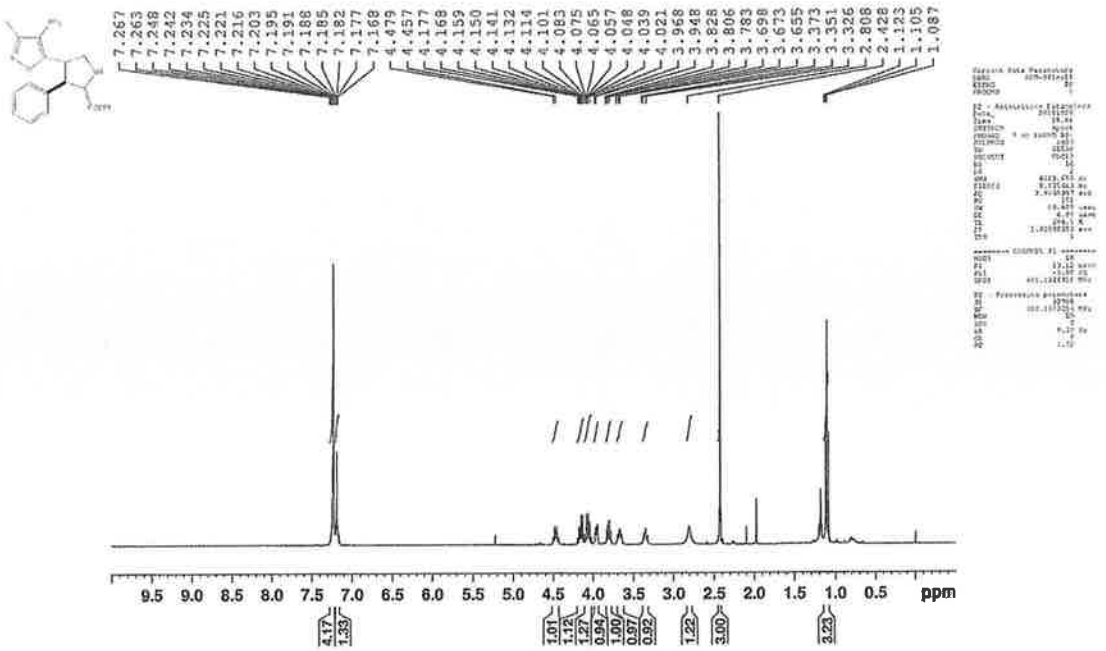
Compound 2.45

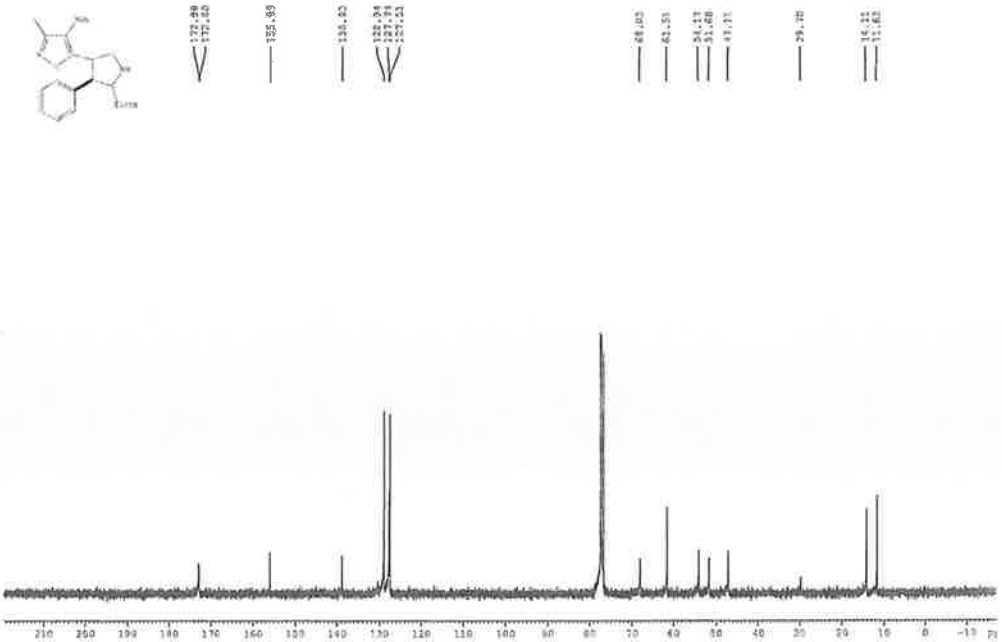


Compound 2.46

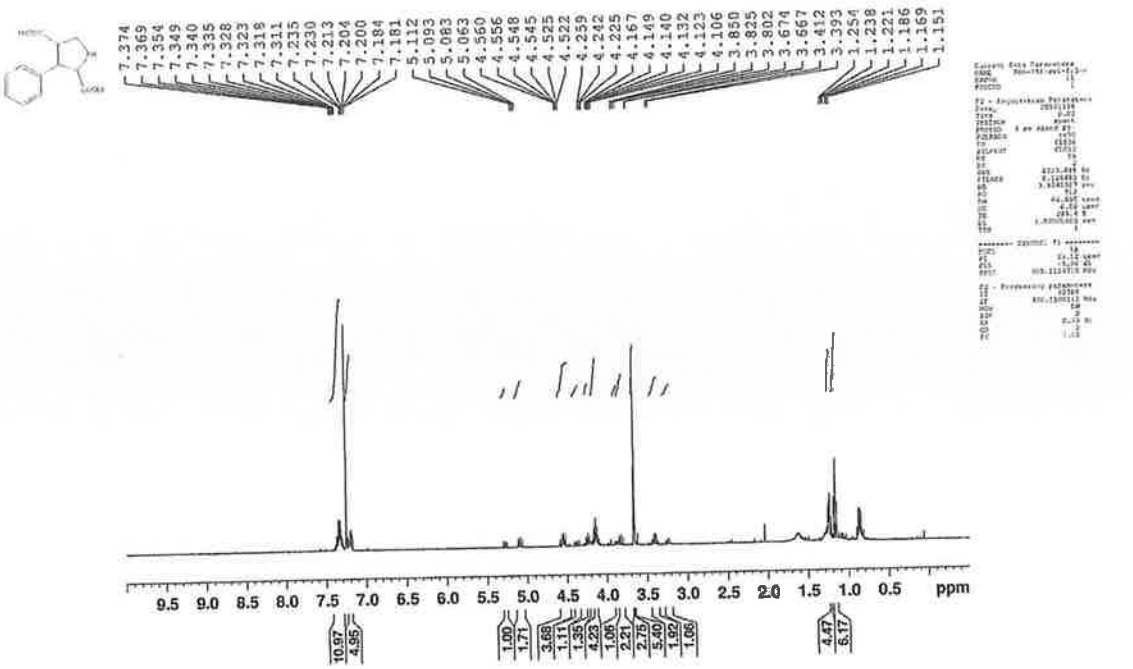


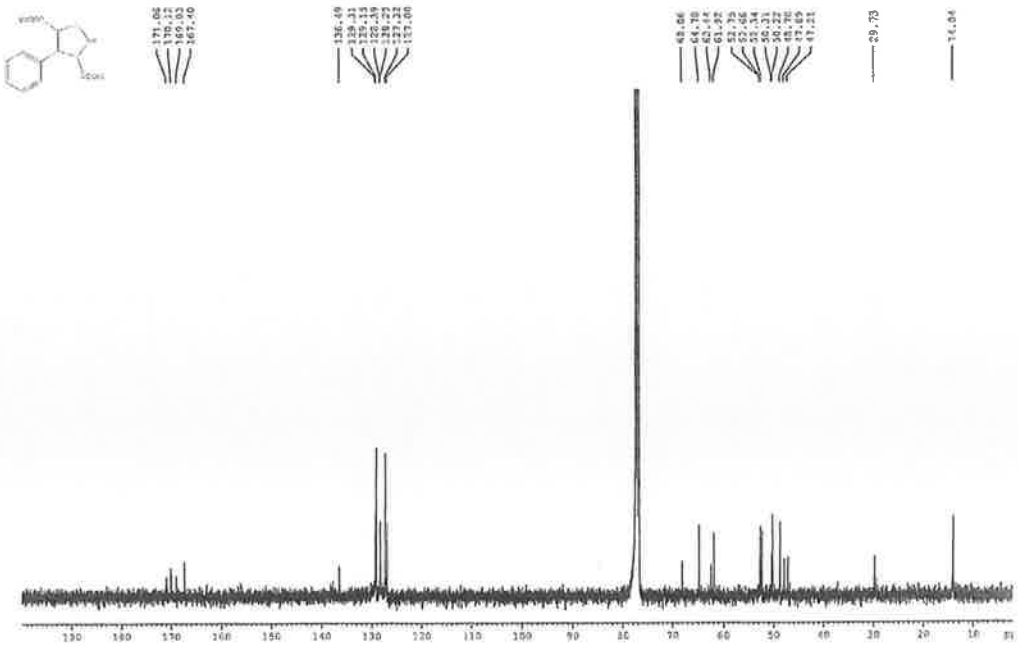
Compound 2.47





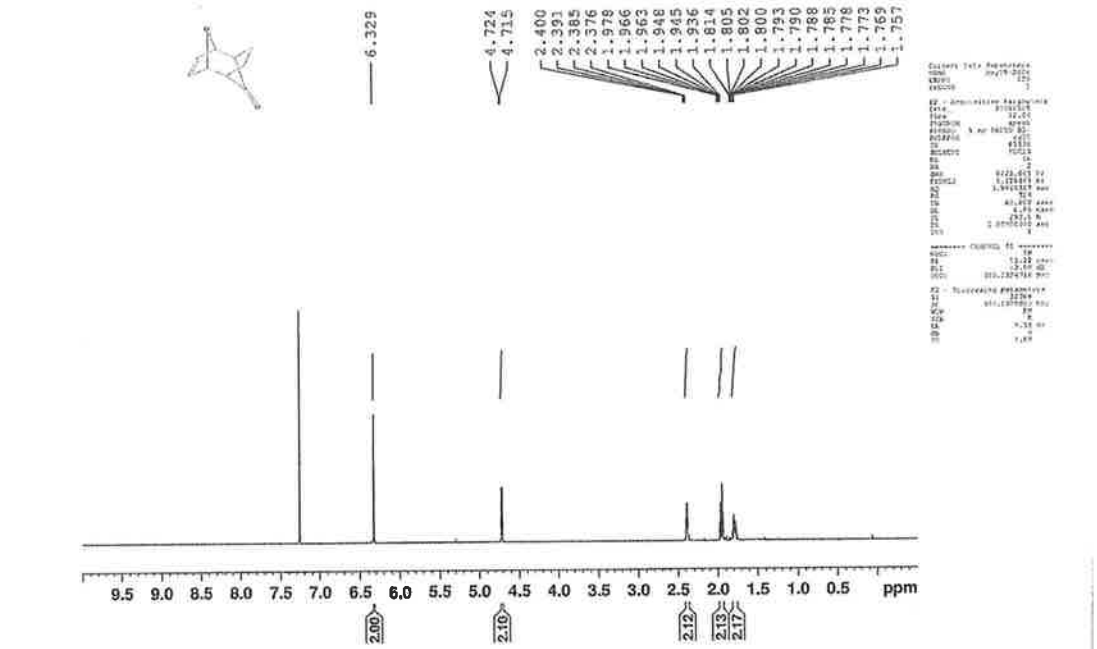
Compound 2.48

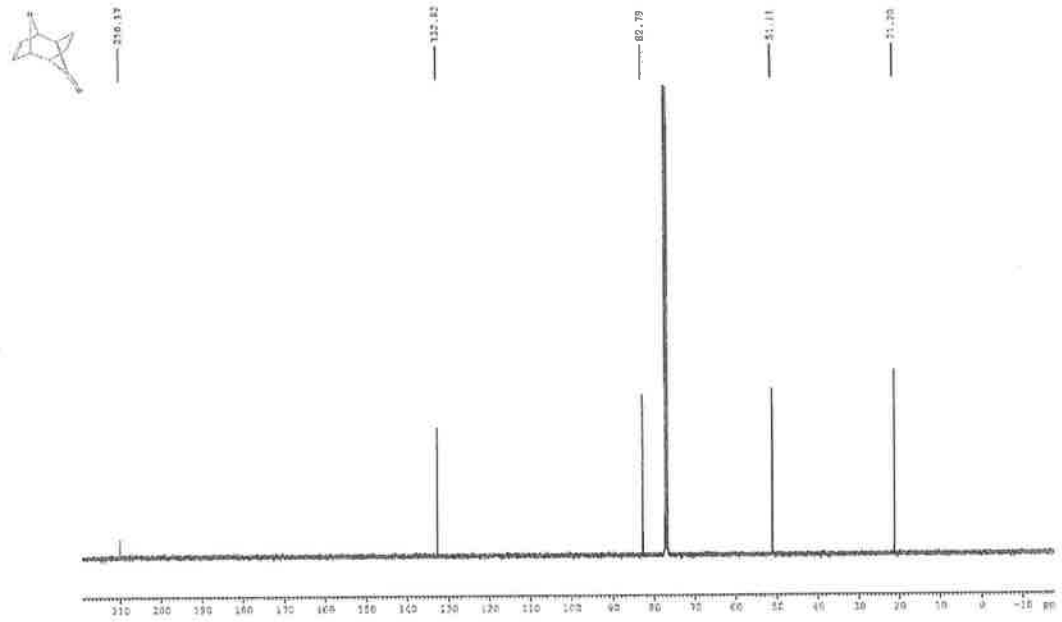




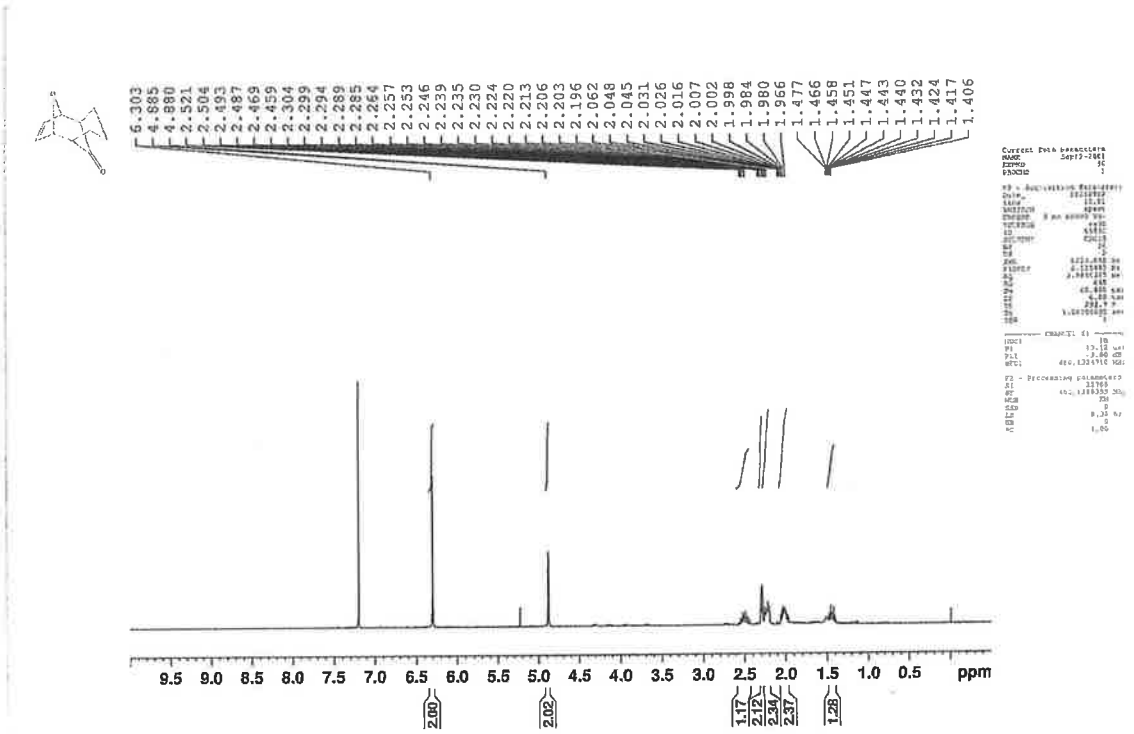
Copies of the ^{1}H NMR and ^{13}C NMR spectra for Chapter 3.

Compound 3.35a

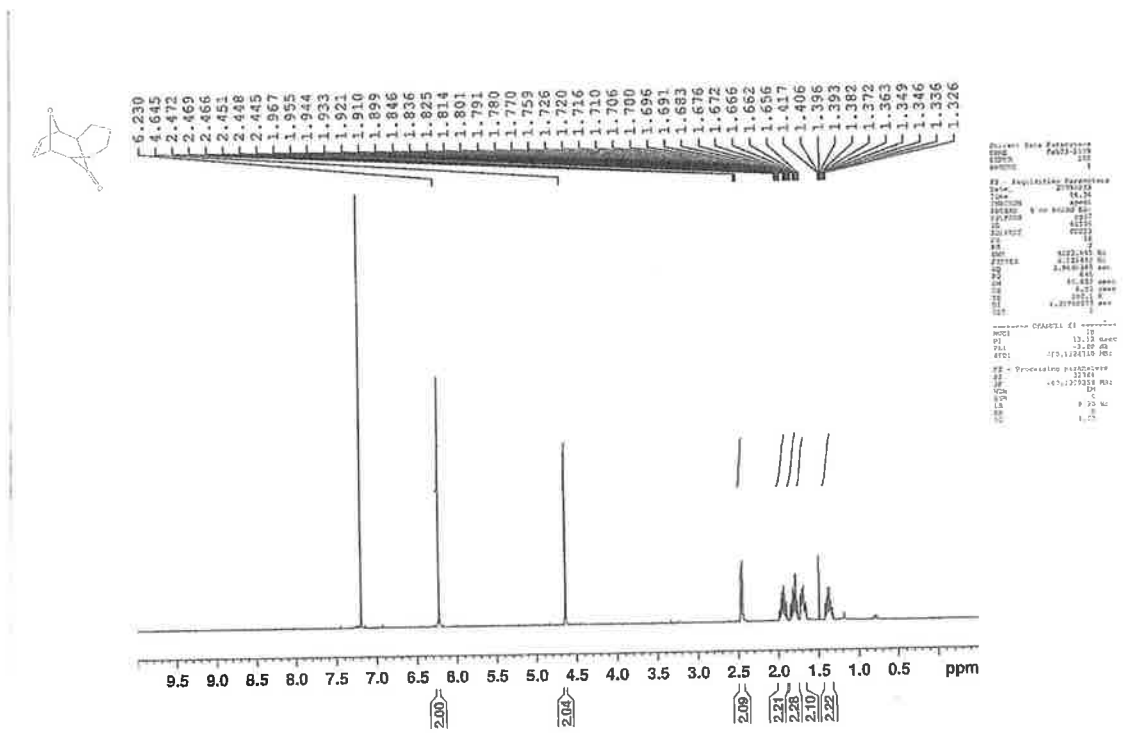


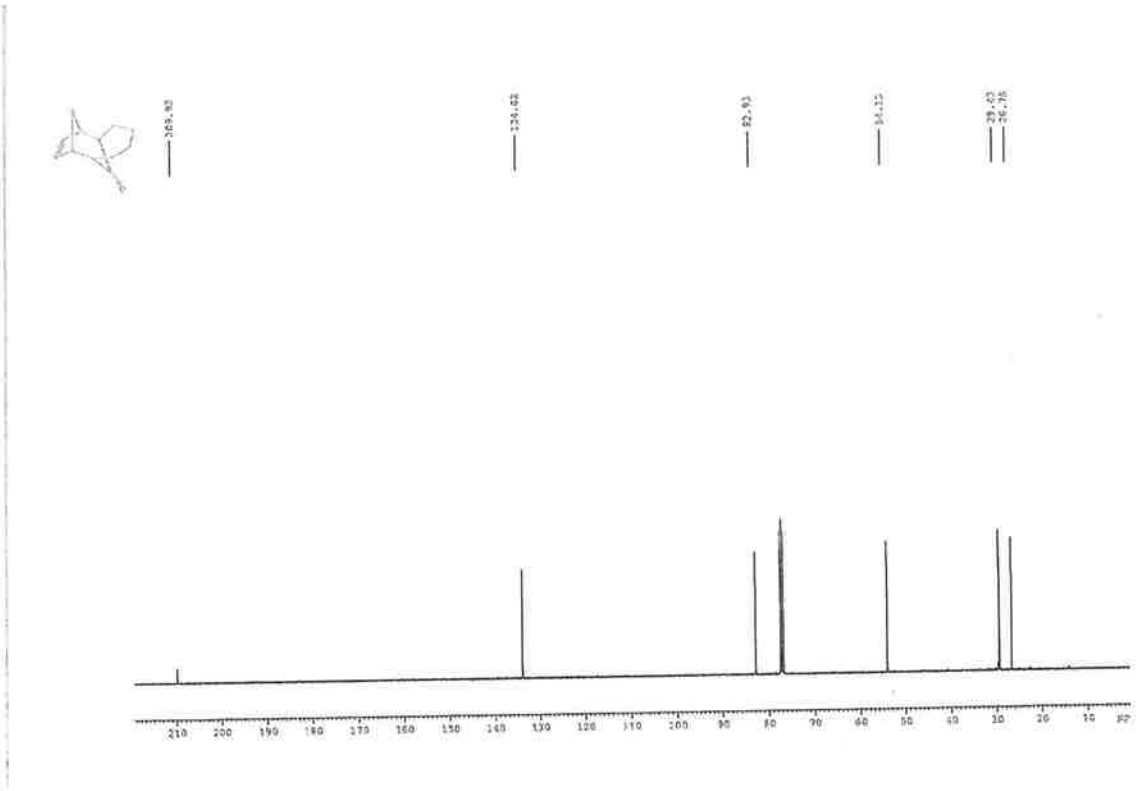


Compound 3.35b

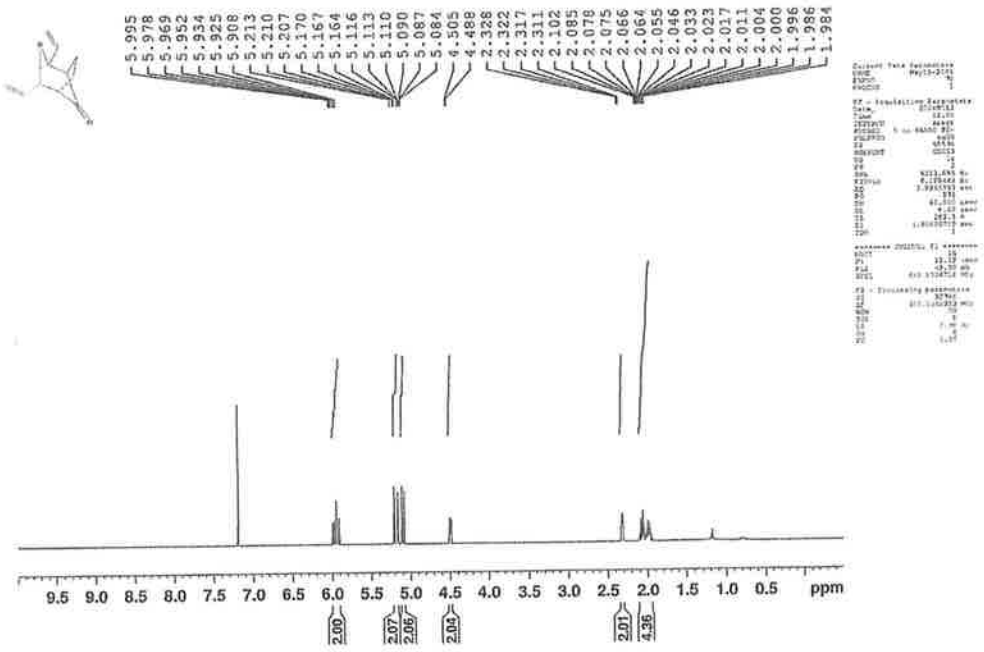


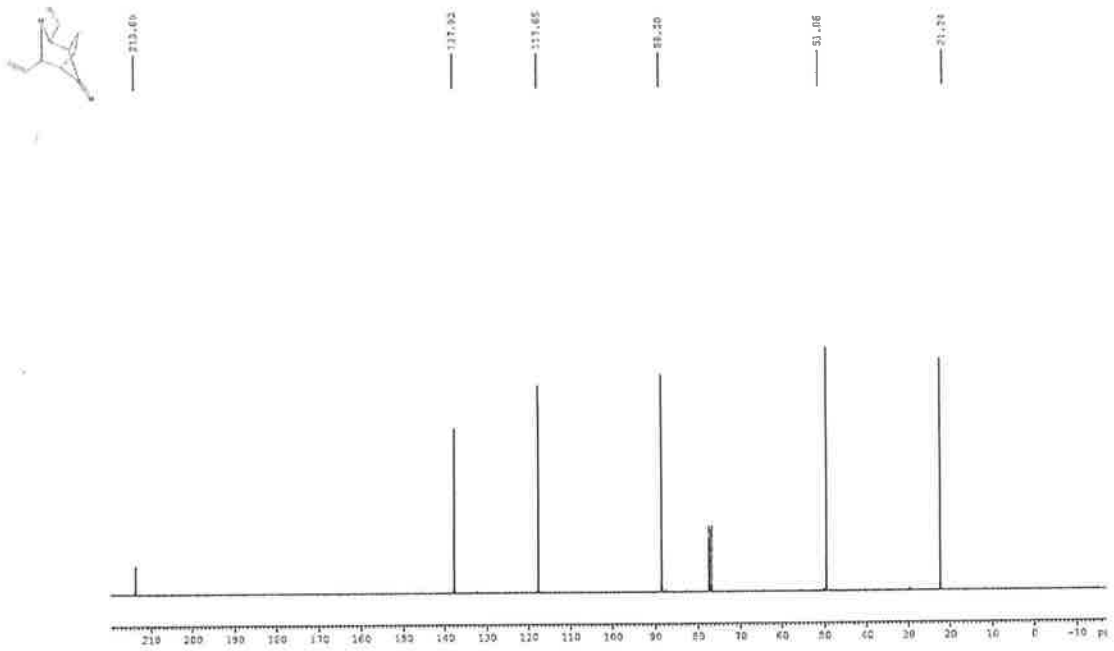
Compound 3.35c



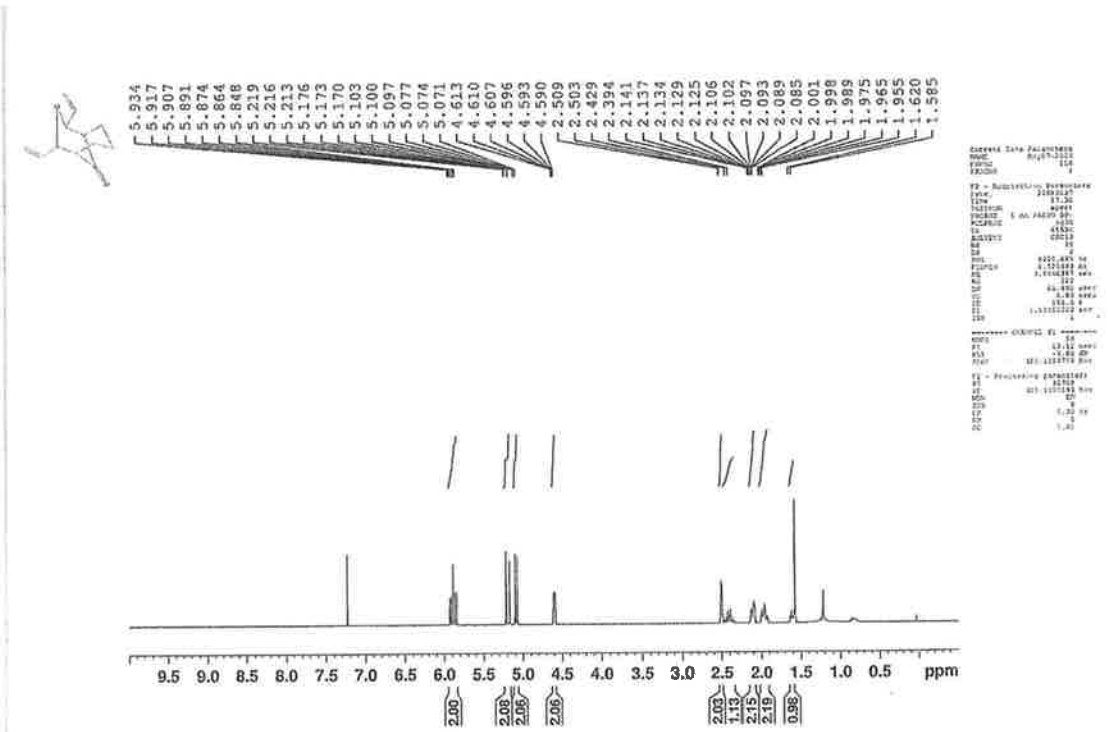


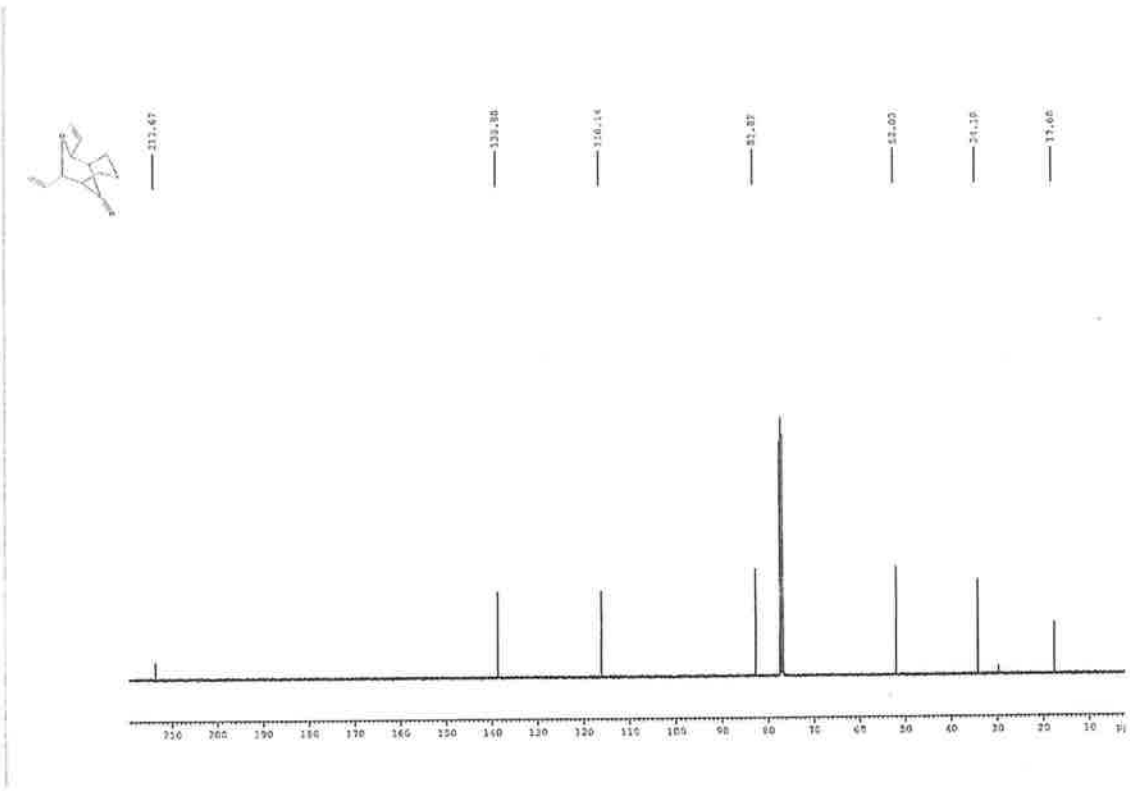
Compound 3.40a



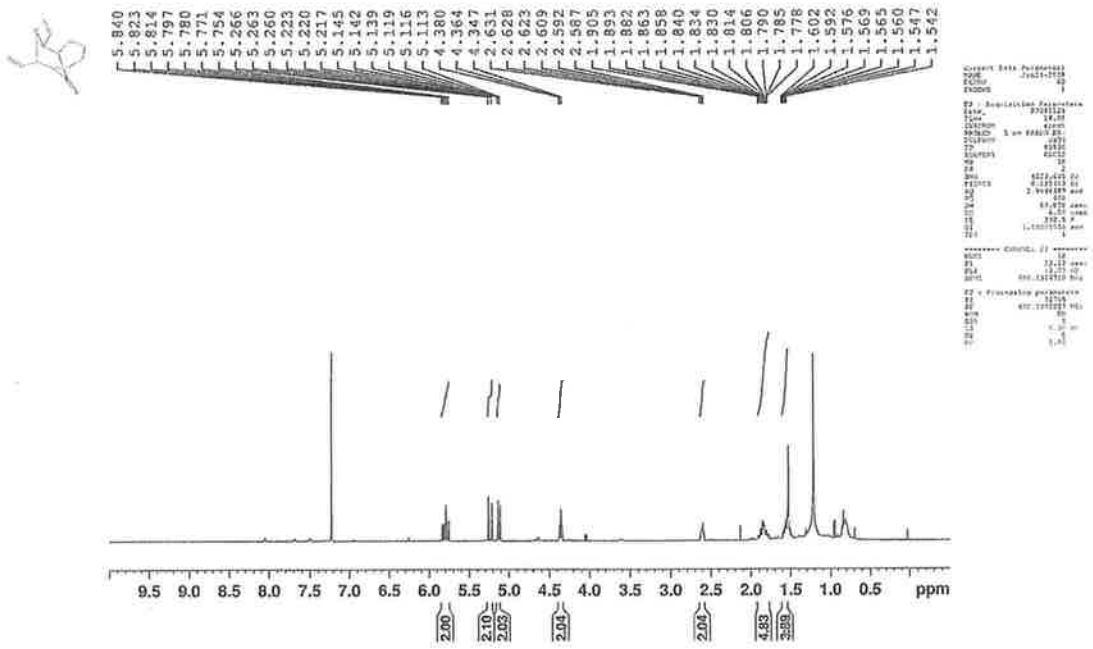


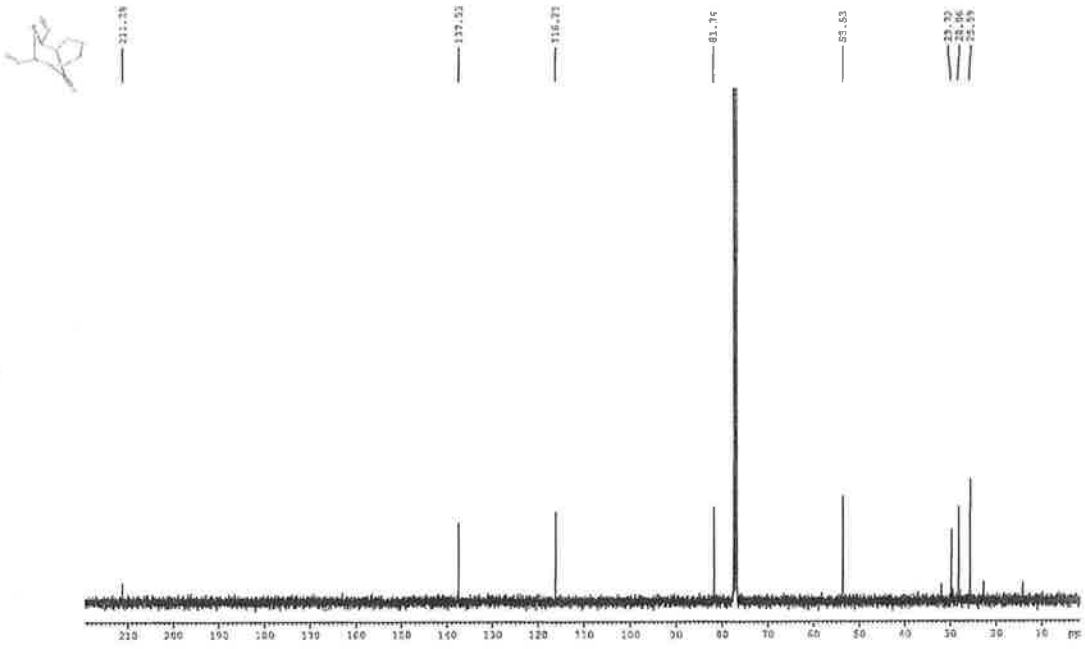
Compound 3.40b



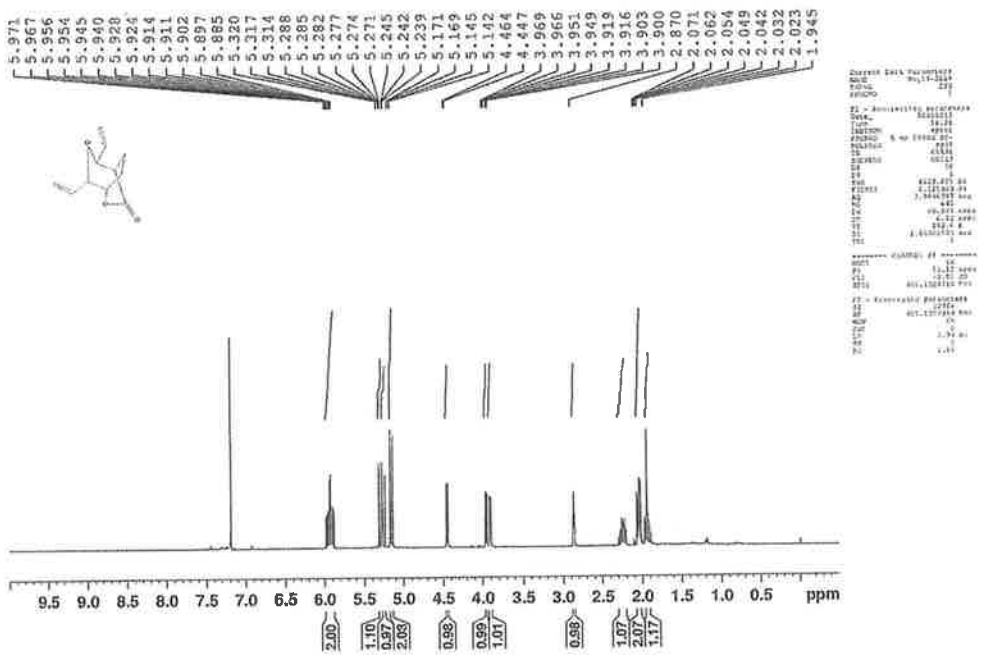


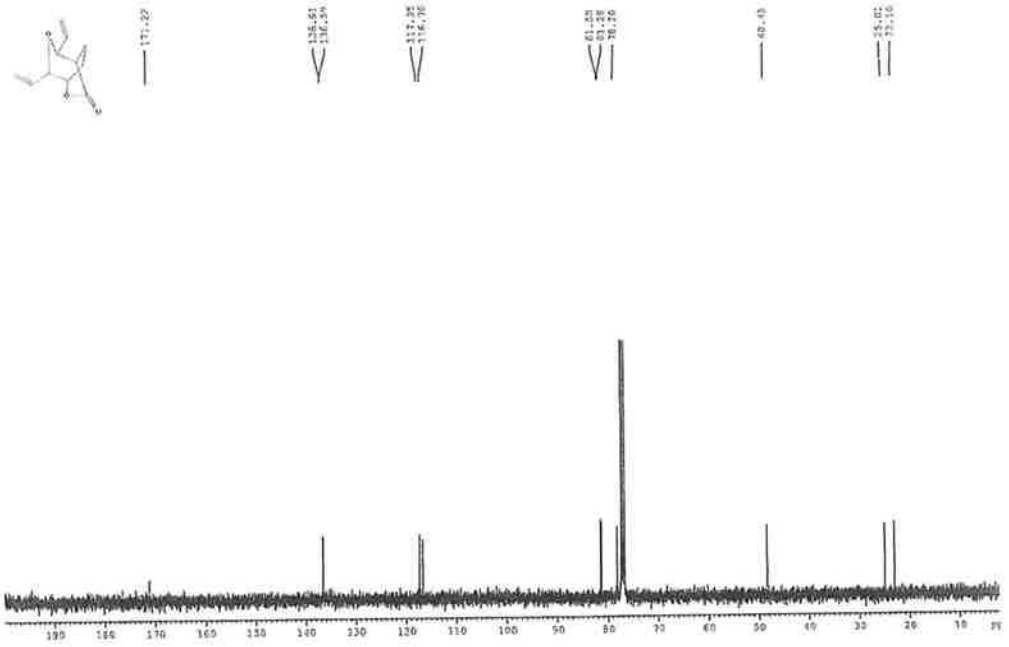
Compound 3.40c



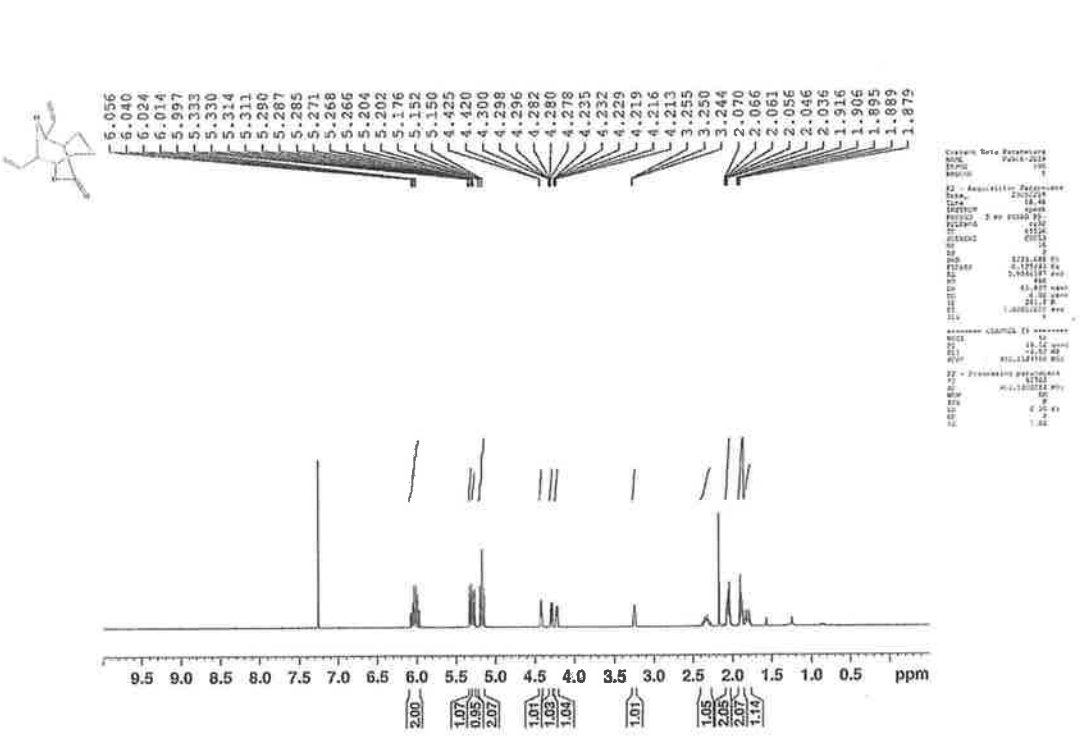


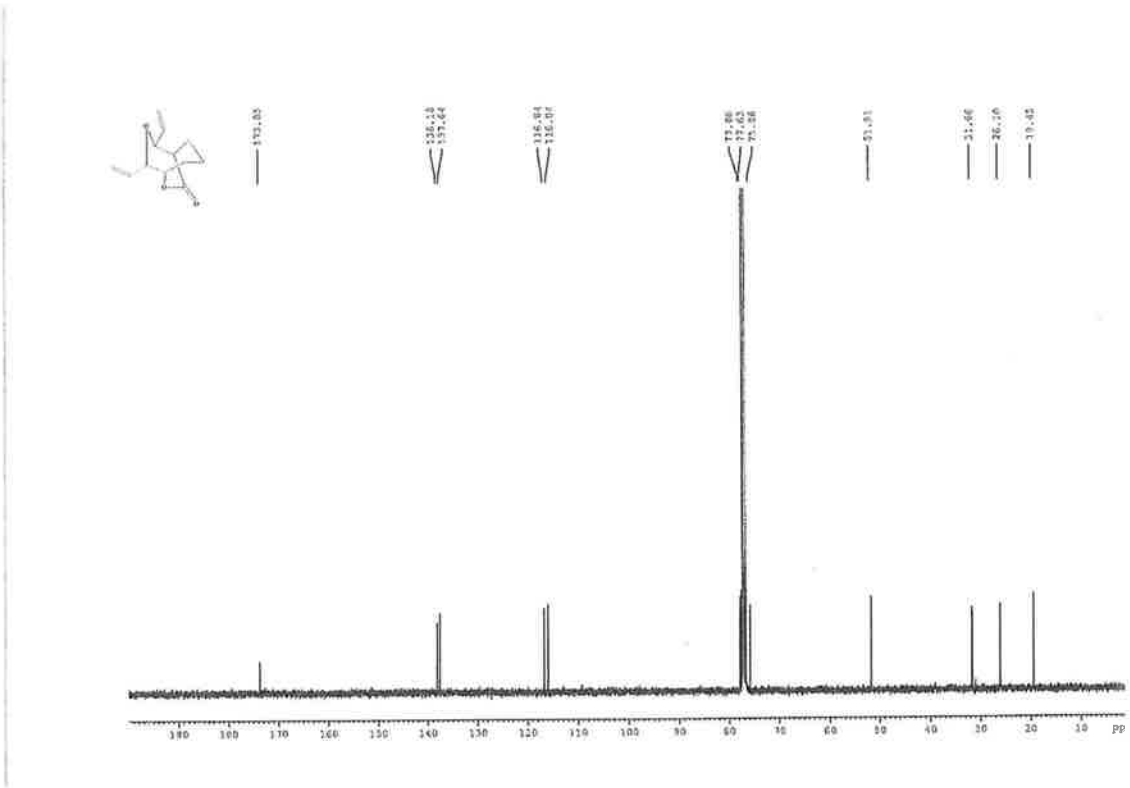
Compound 3.41a



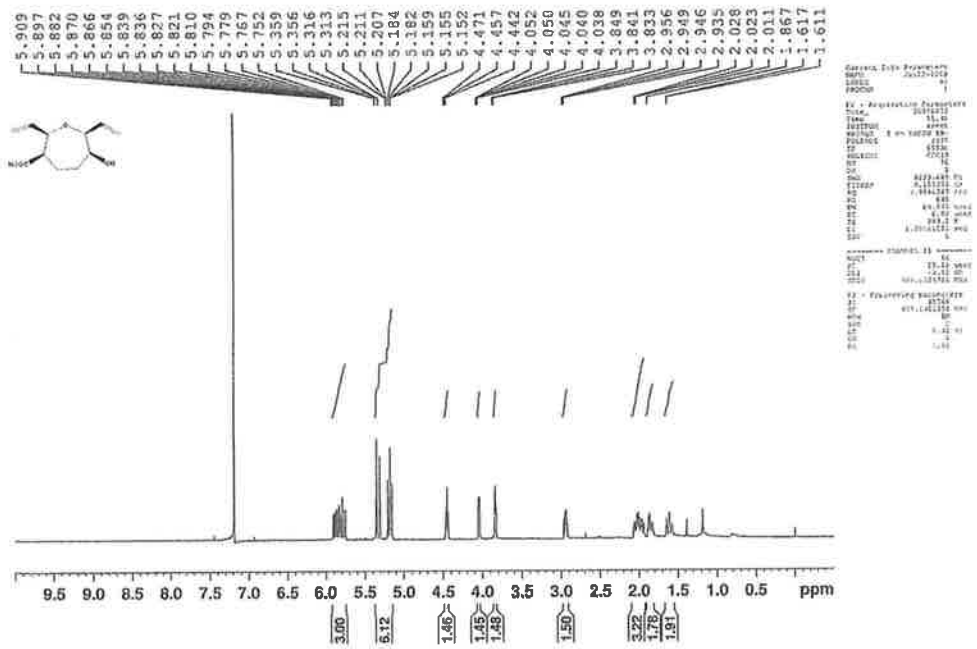


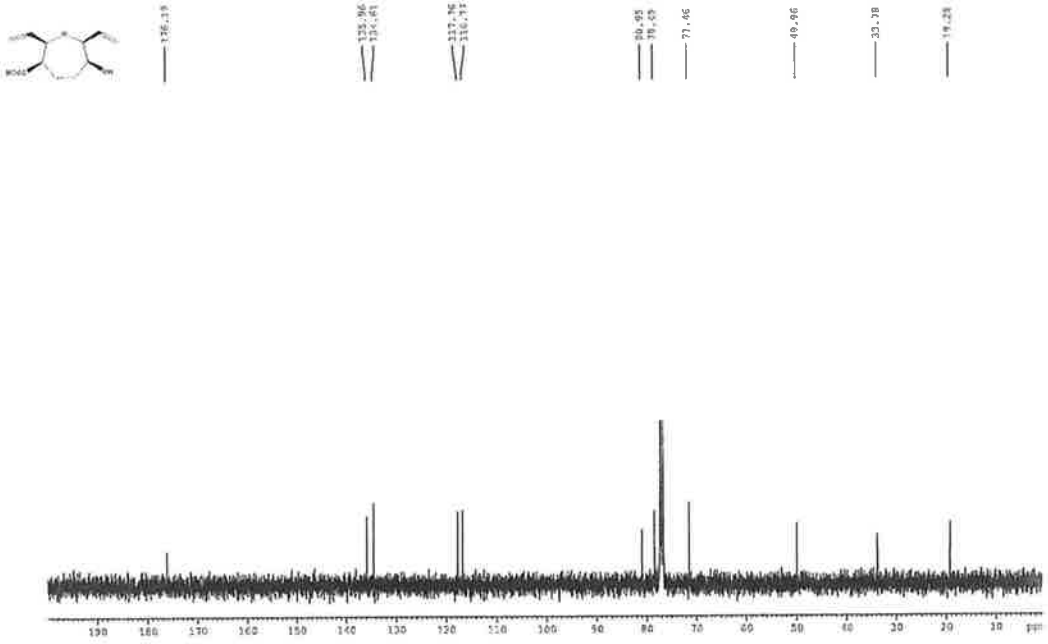
Compound 3.41b



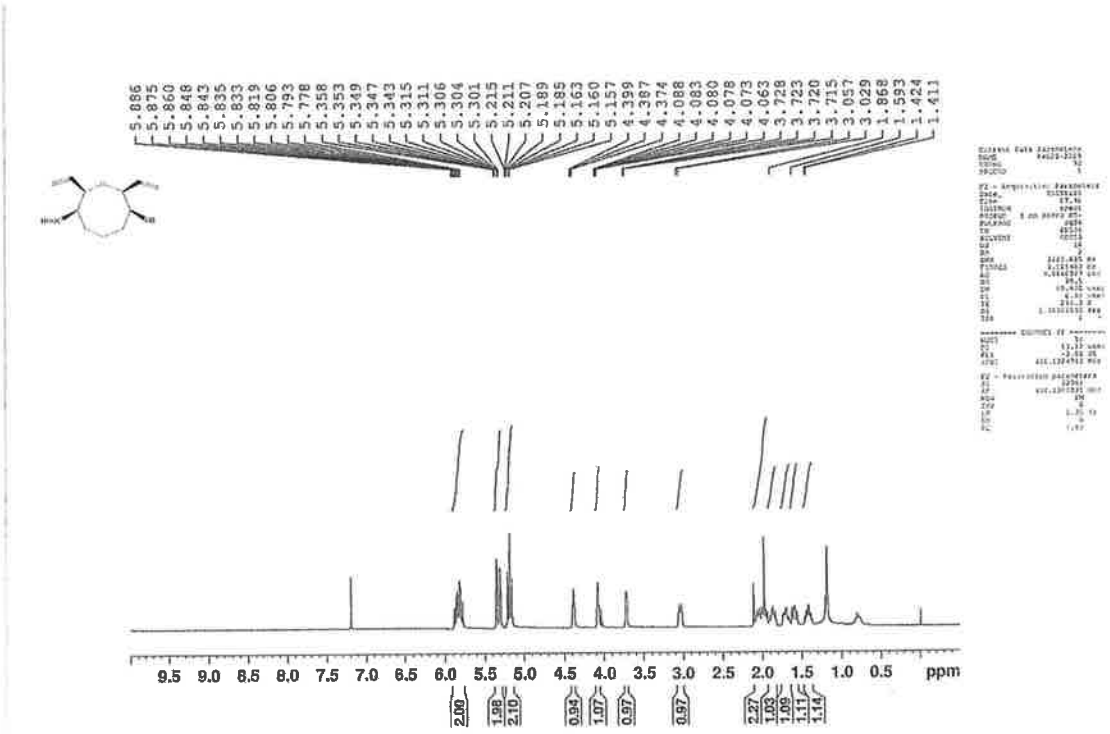


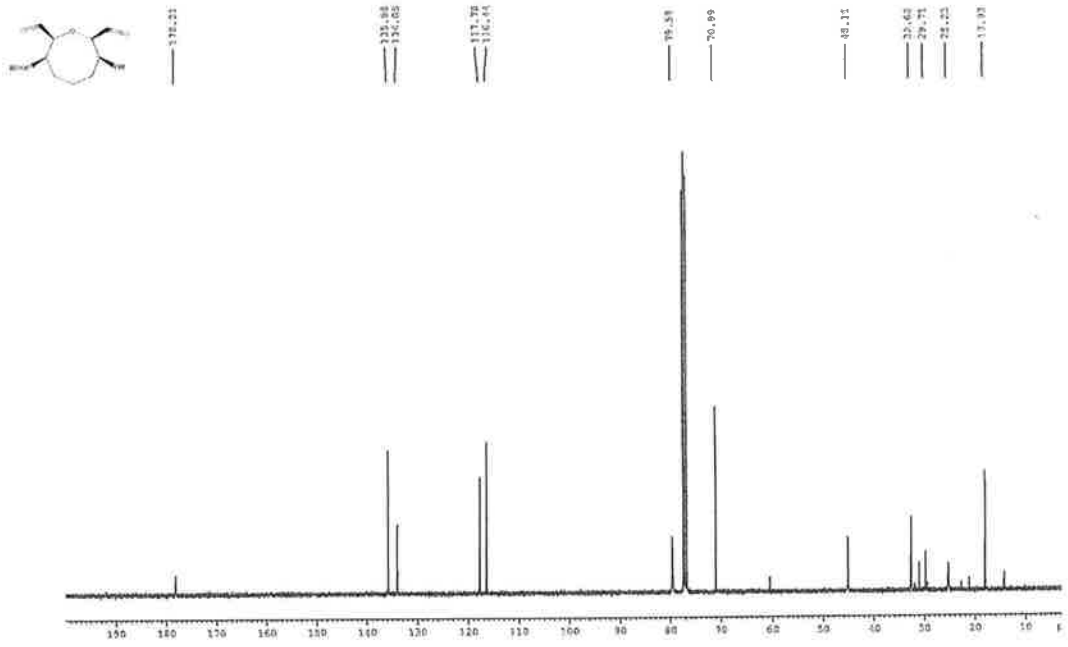
Compound 3.42a

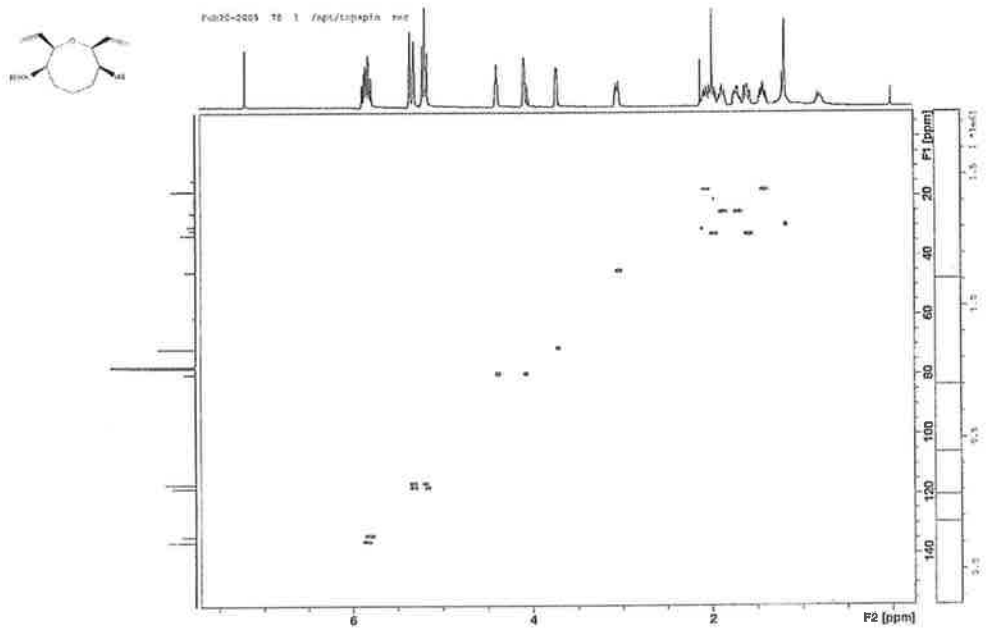


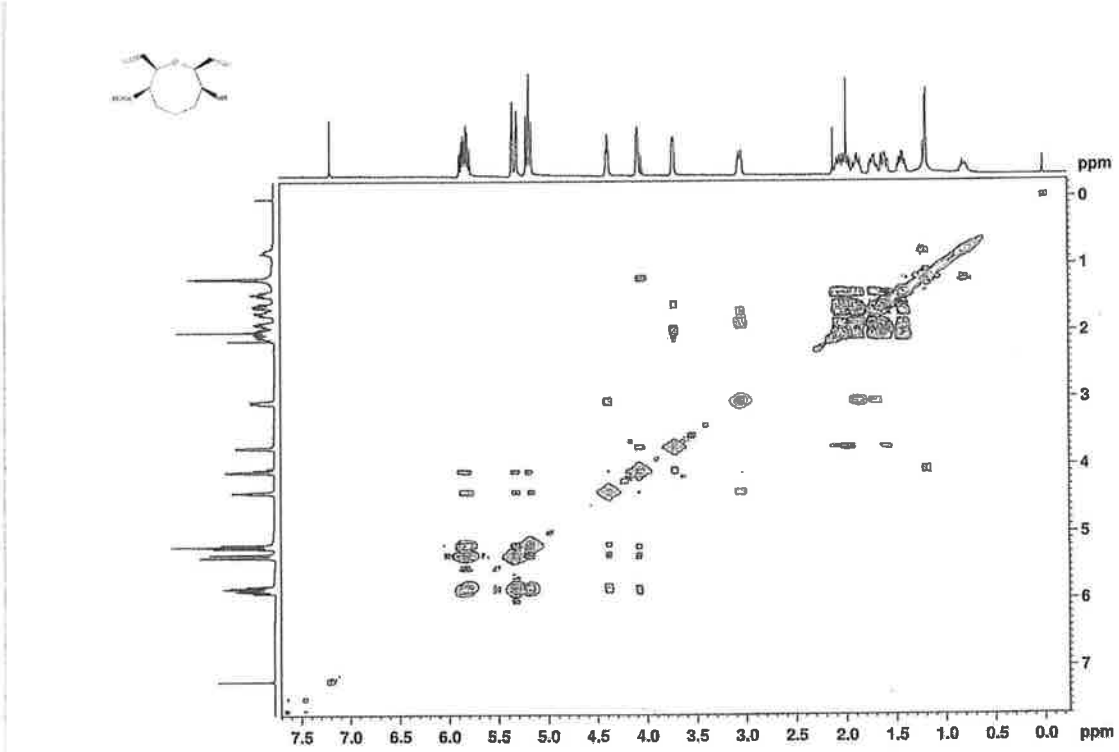


Compound 3.42b

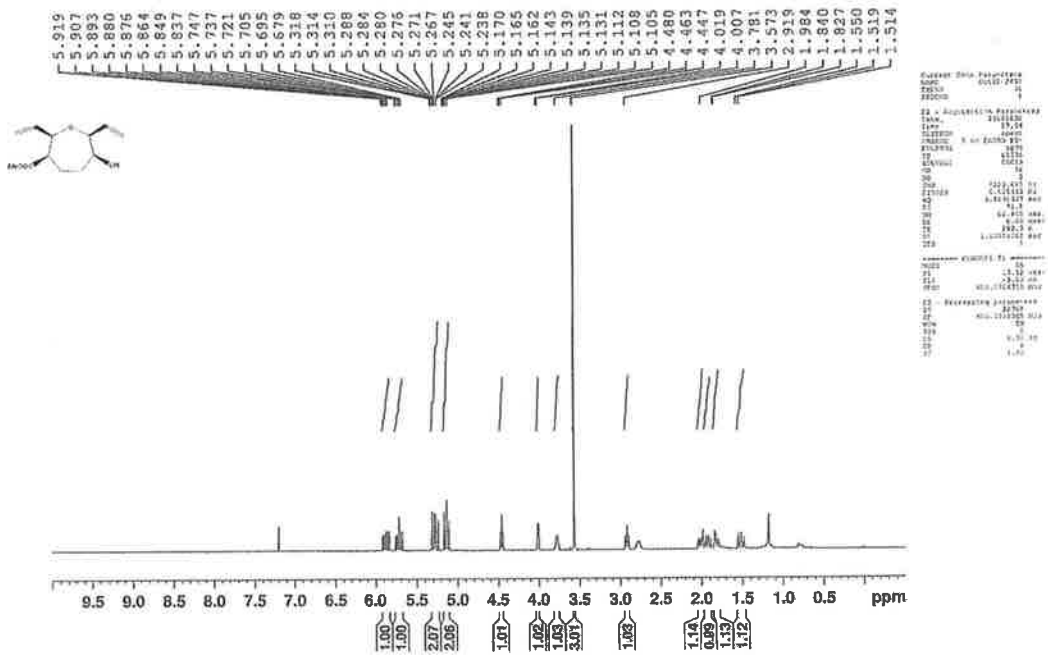


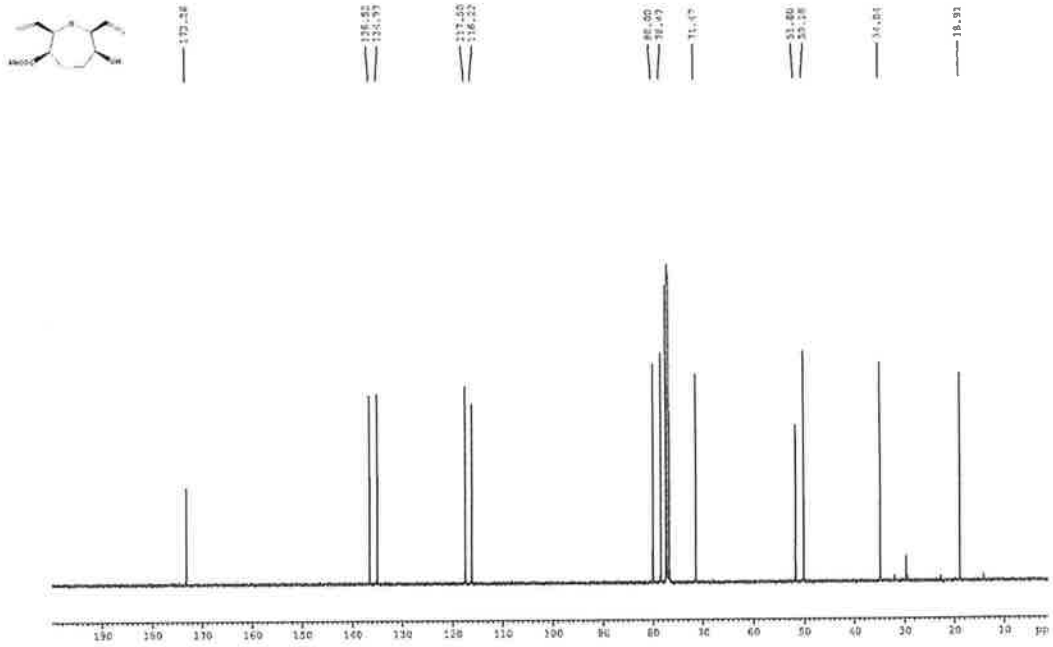


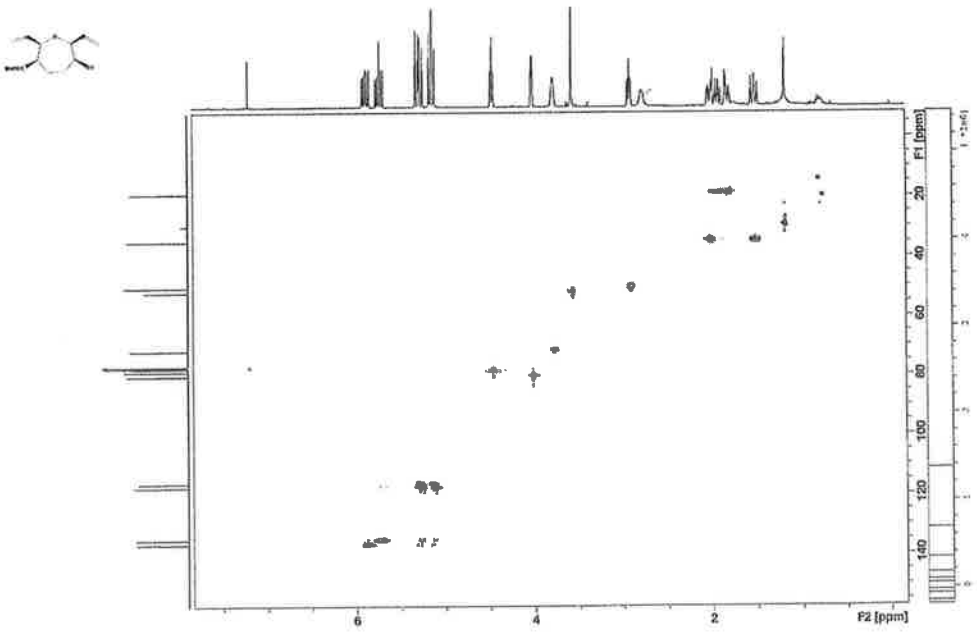

F1 (ppm)
F2 (ppm)

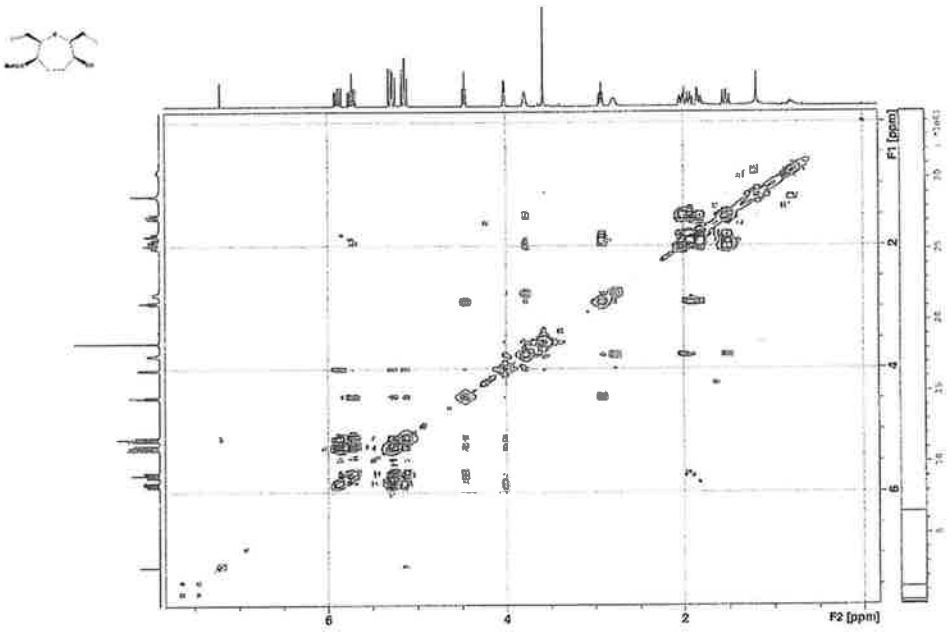


Compound 3.43

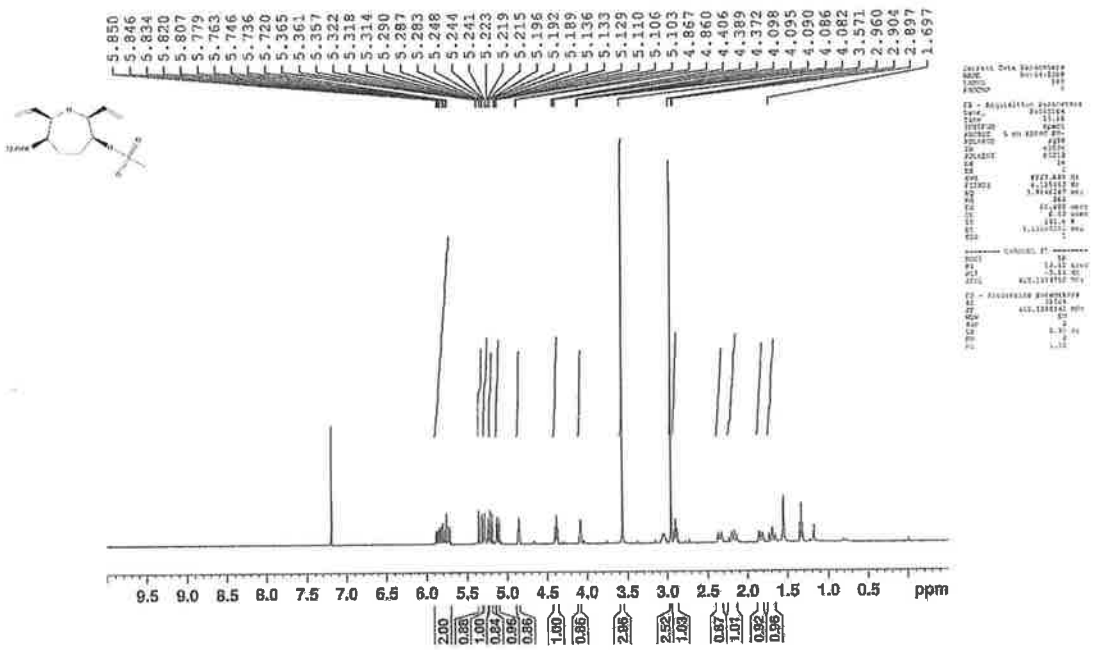




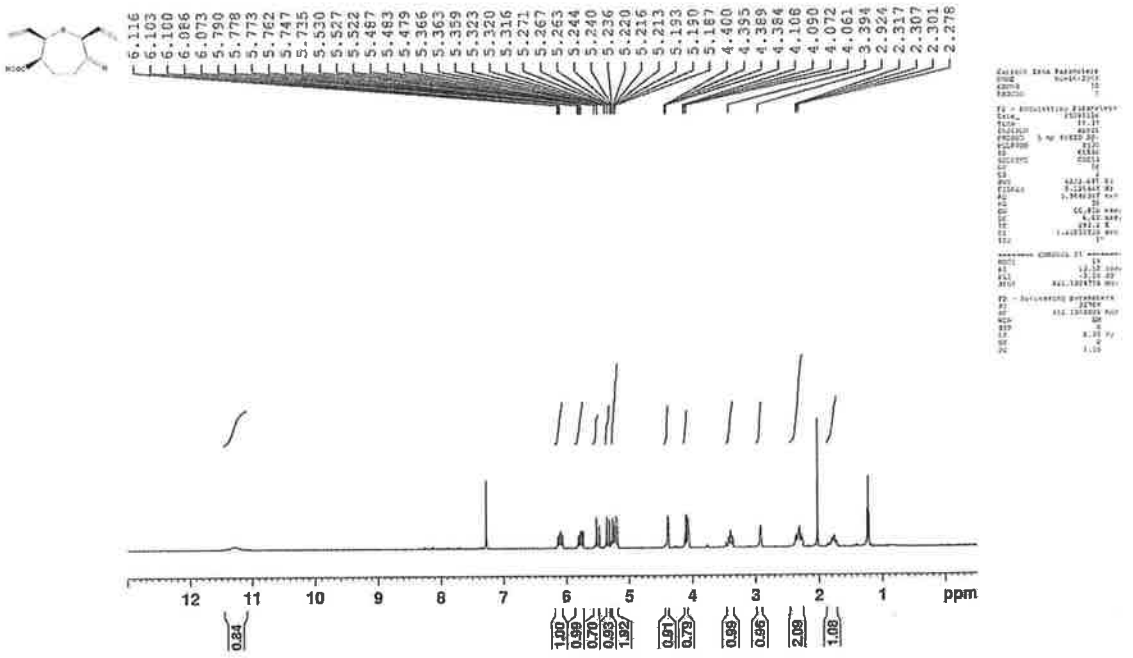

F1 [ppm]
F2 [ppm]

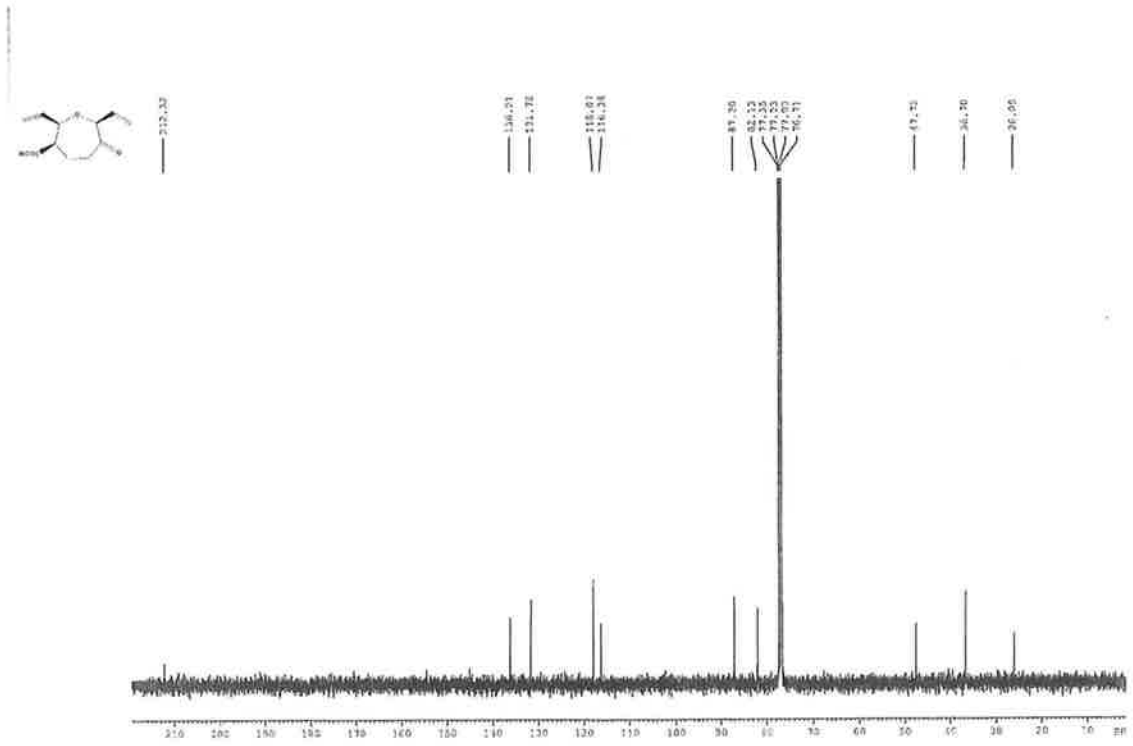


Compound 3.43e

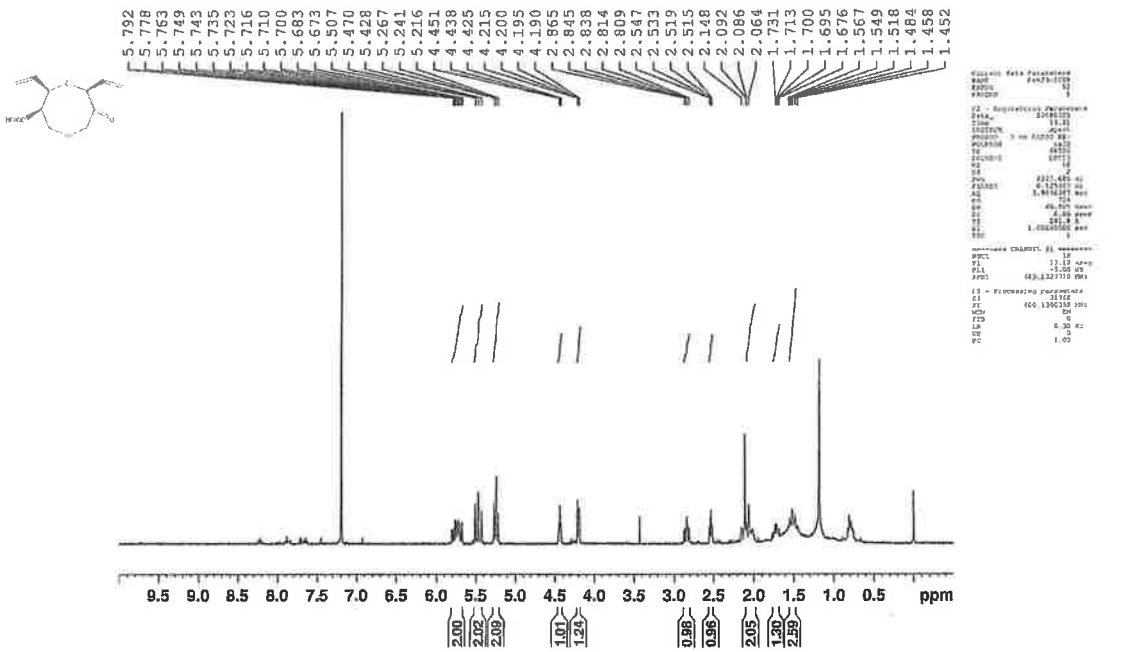


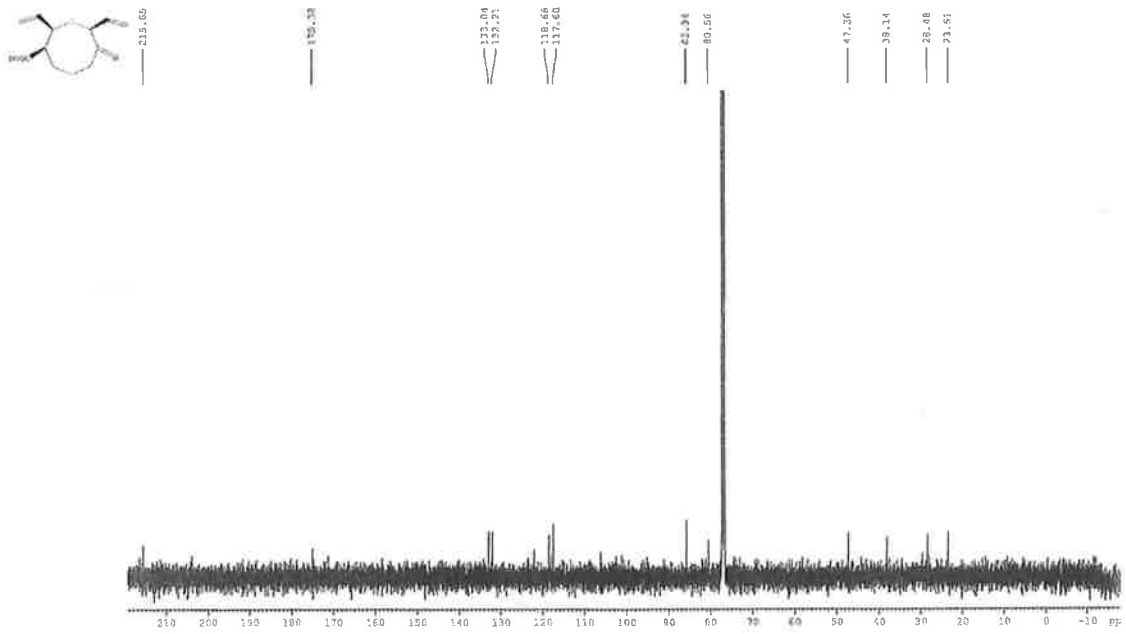
Compound 3.44a



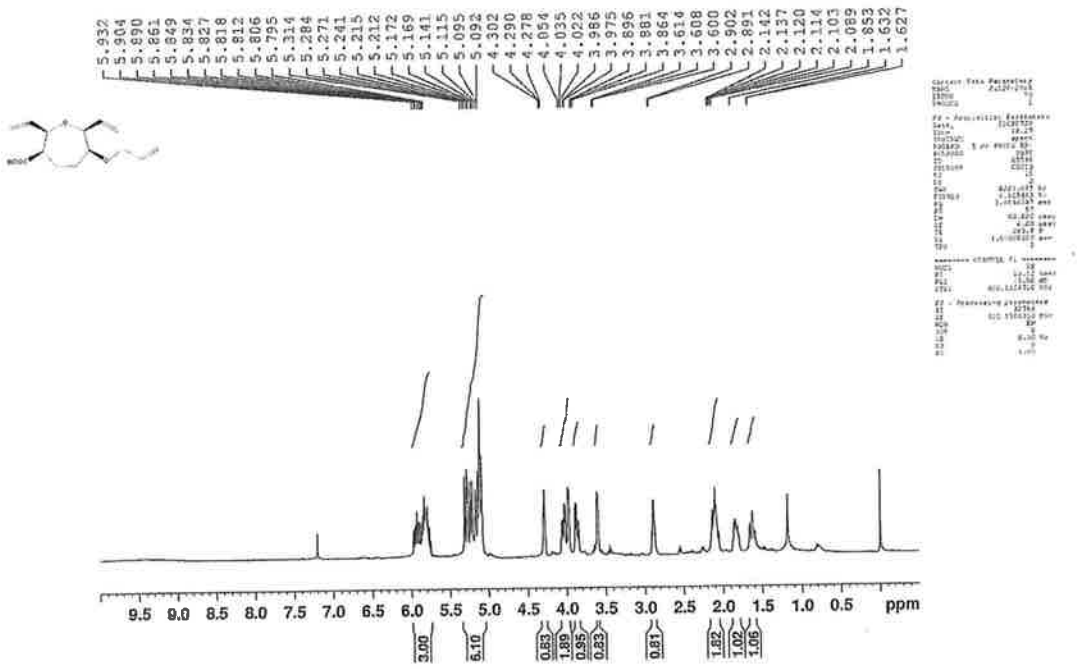


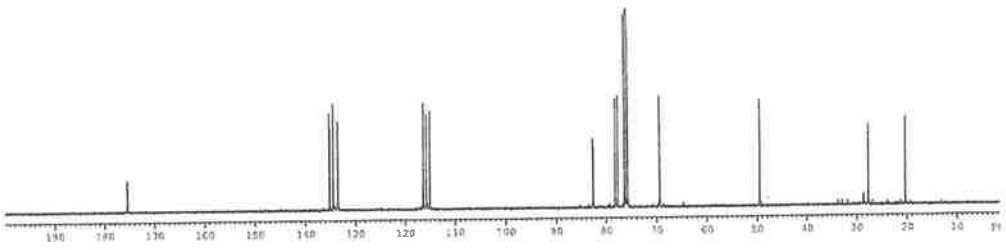
Compound 3.44b



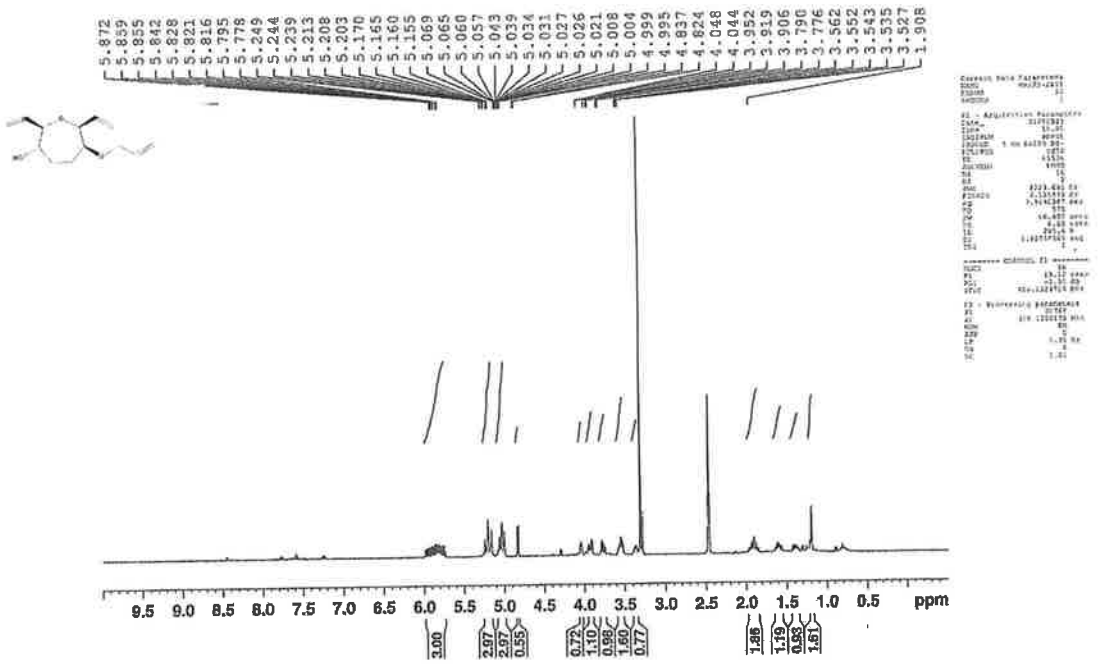


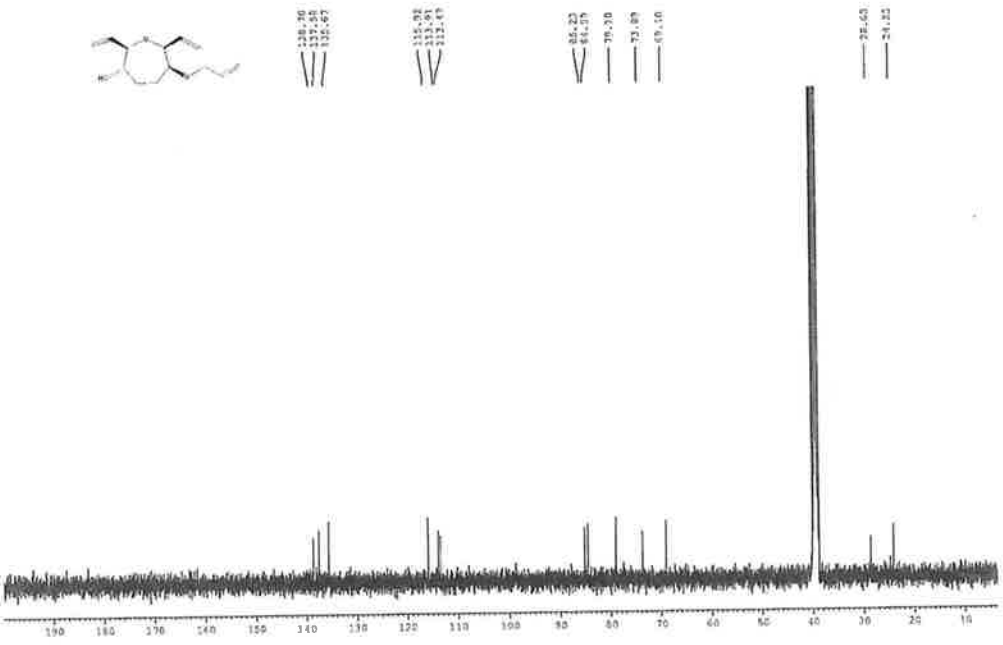
Compound 3.46



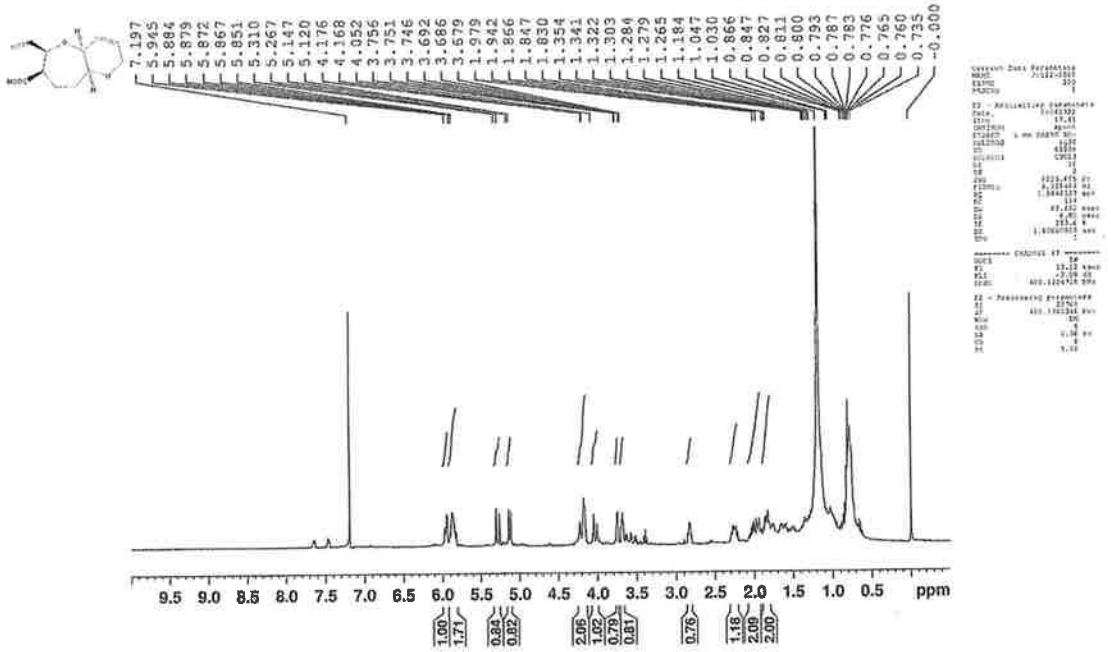


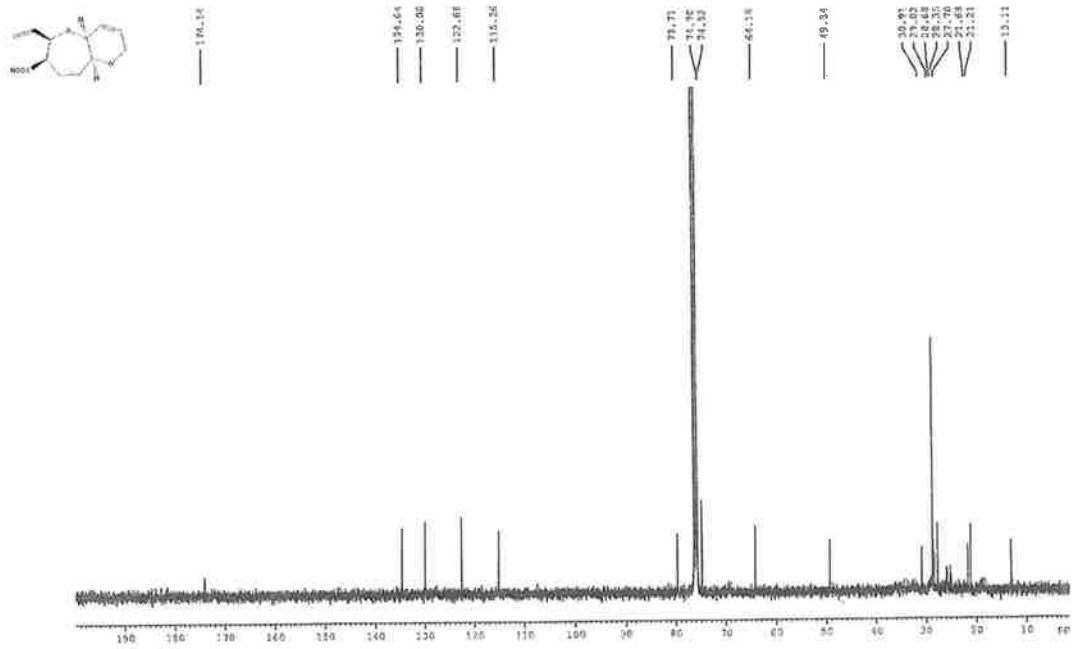
Compound 3.47



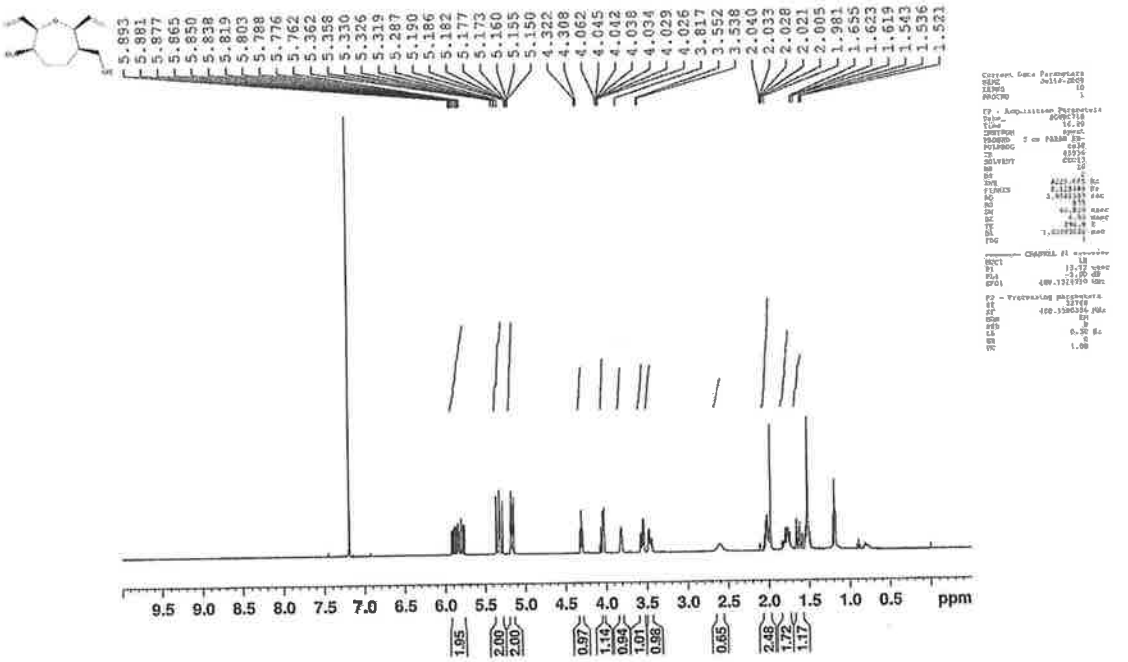


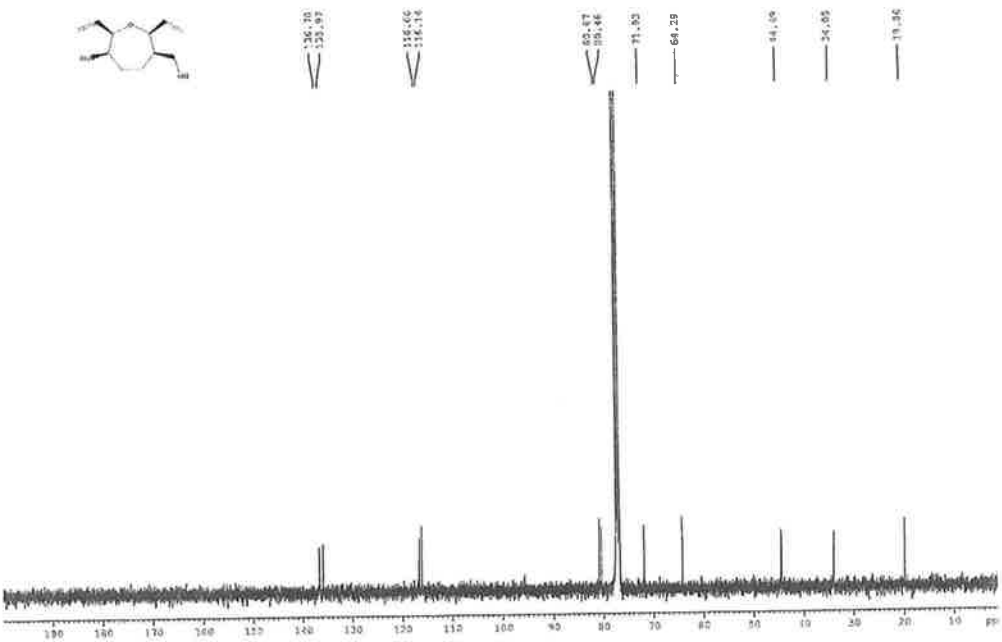
Compound 3.48





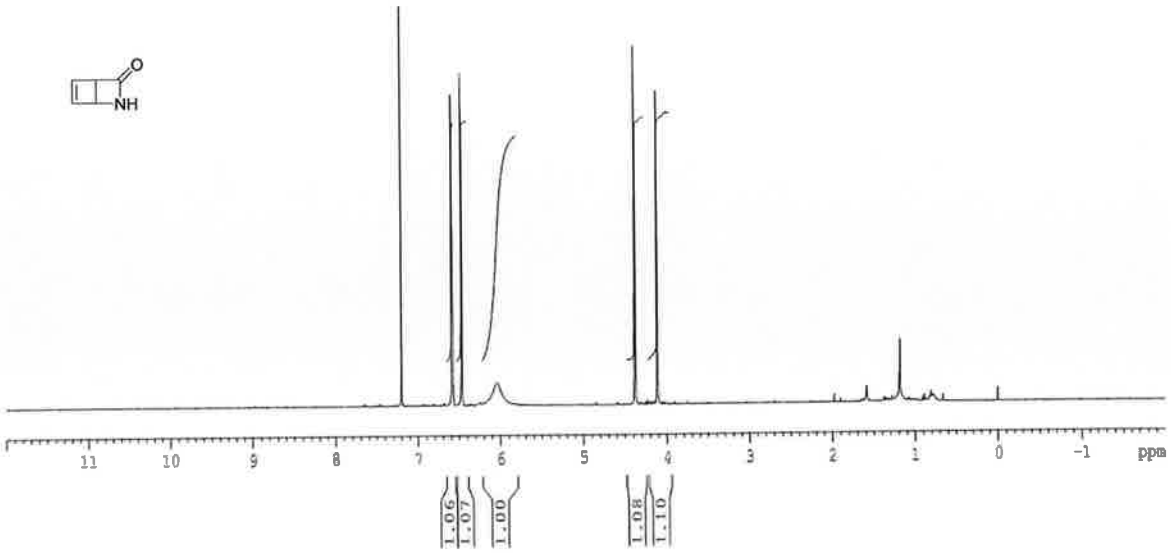
Compound 3.50

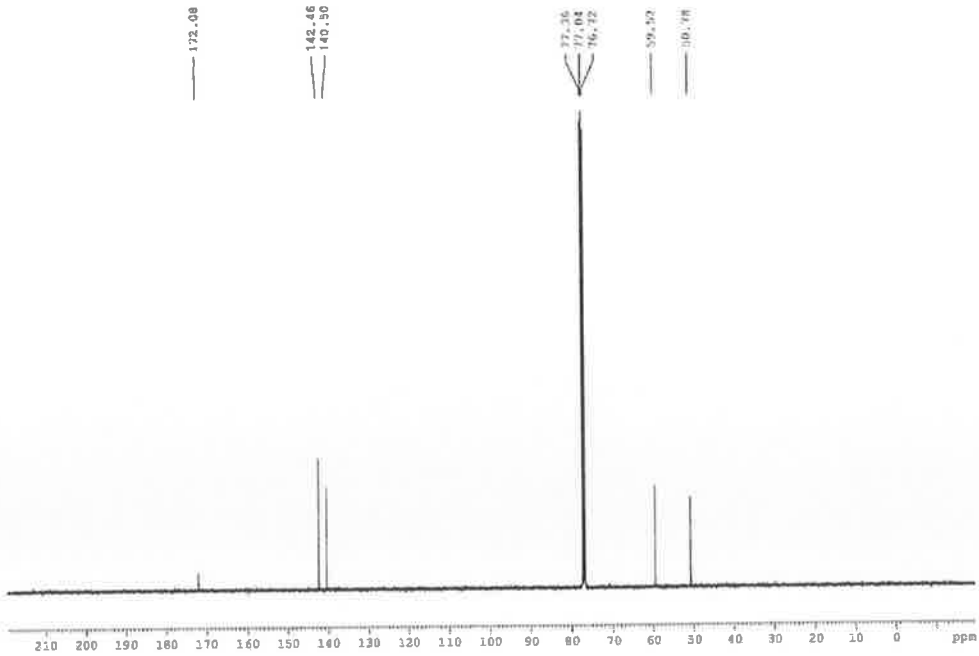




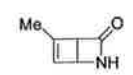
Copies of the ^{1}H NMR and ^{13}C NMR spectra for Chapter 4

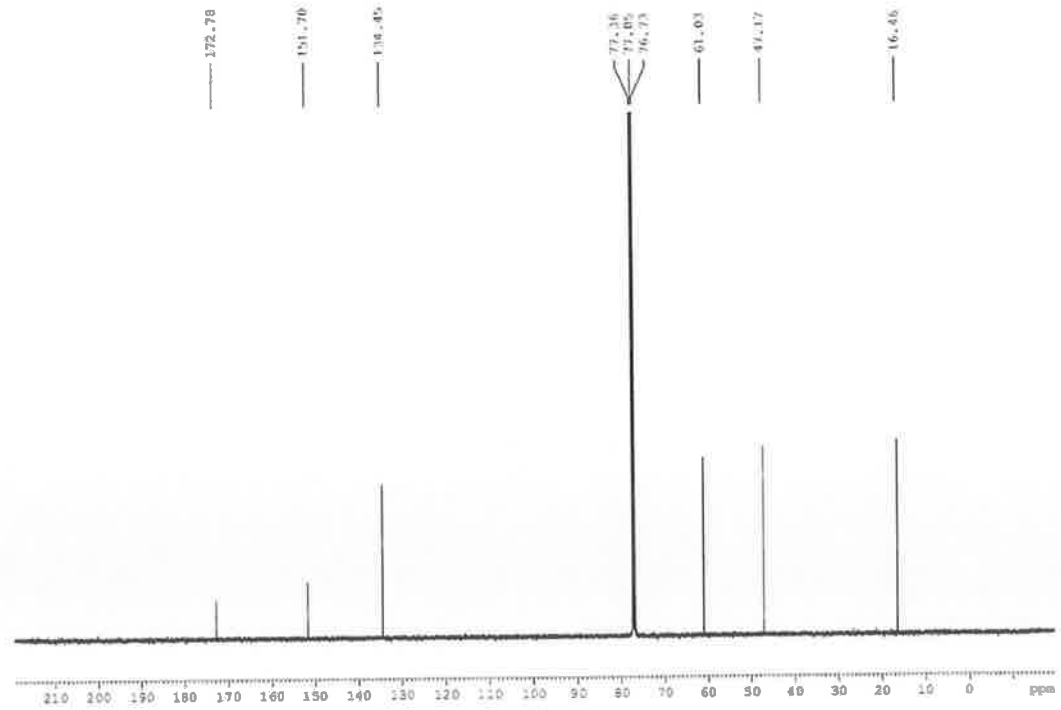
Compound 4.2a



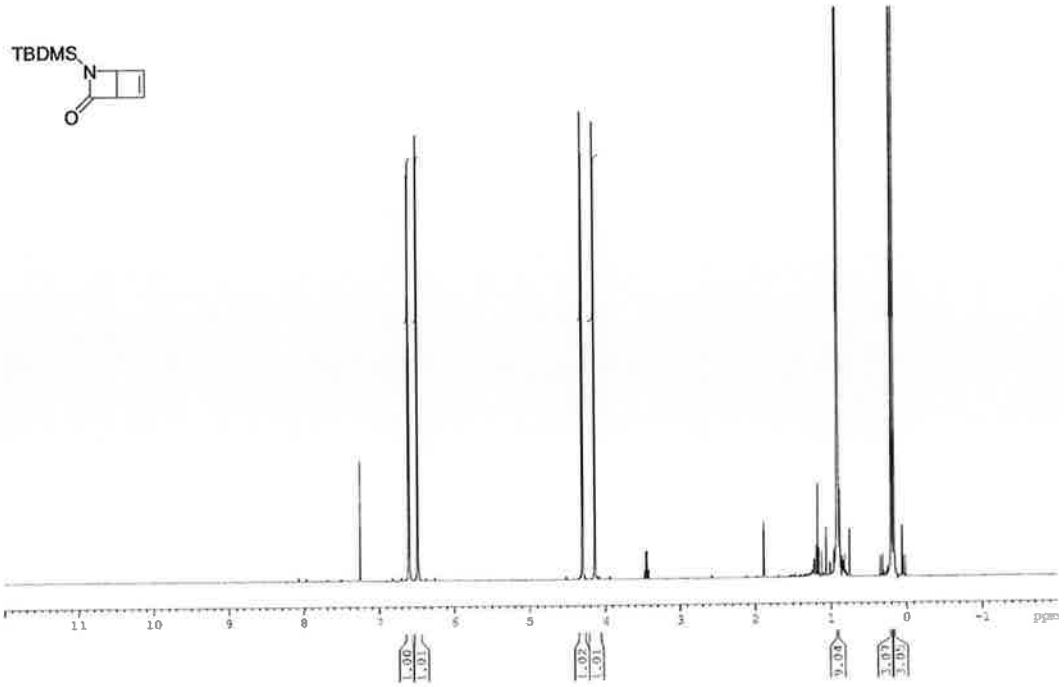


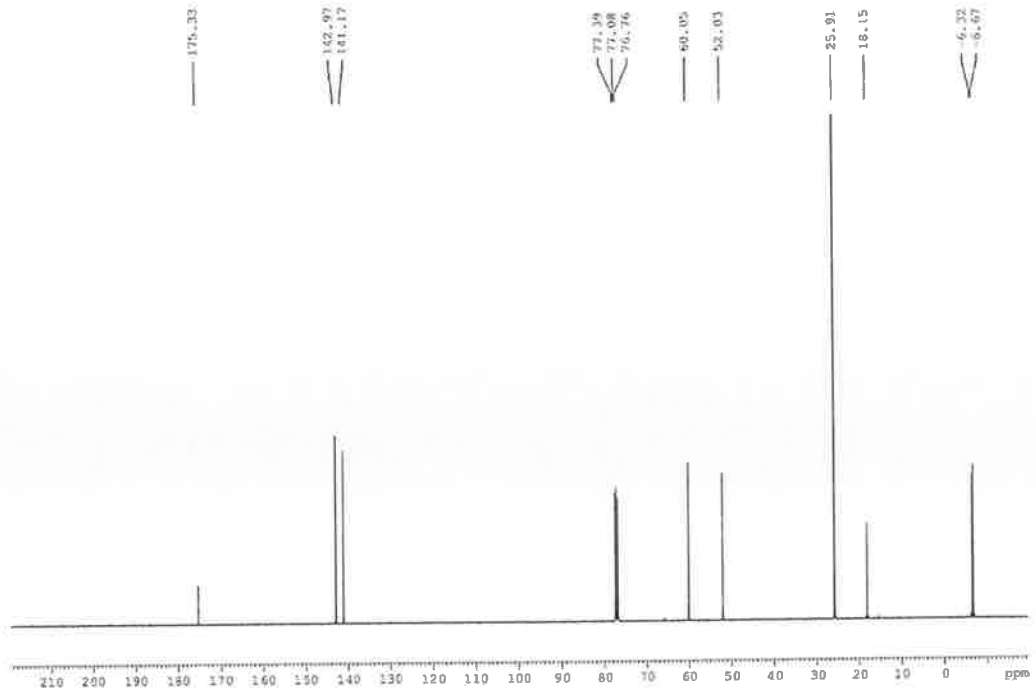
Compound 4.2c



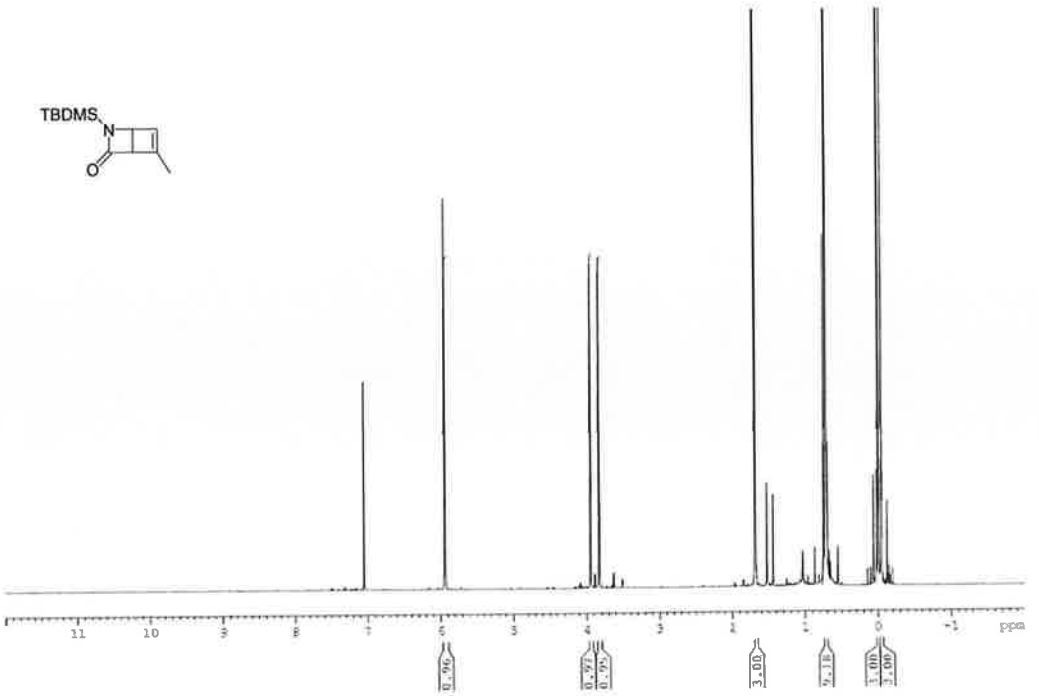


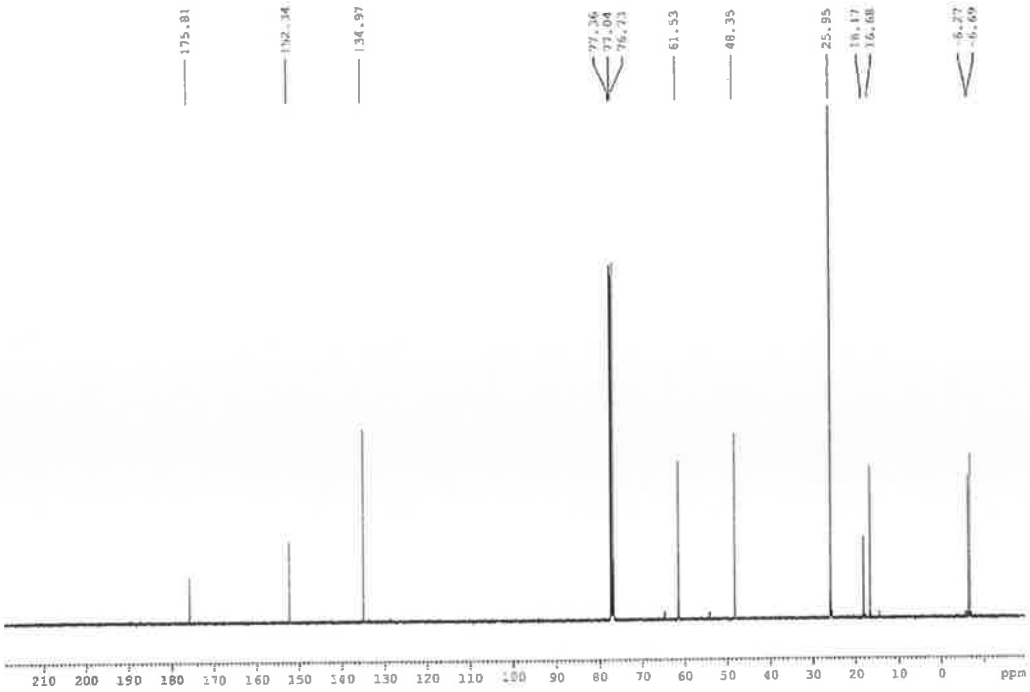
Compound 4.20



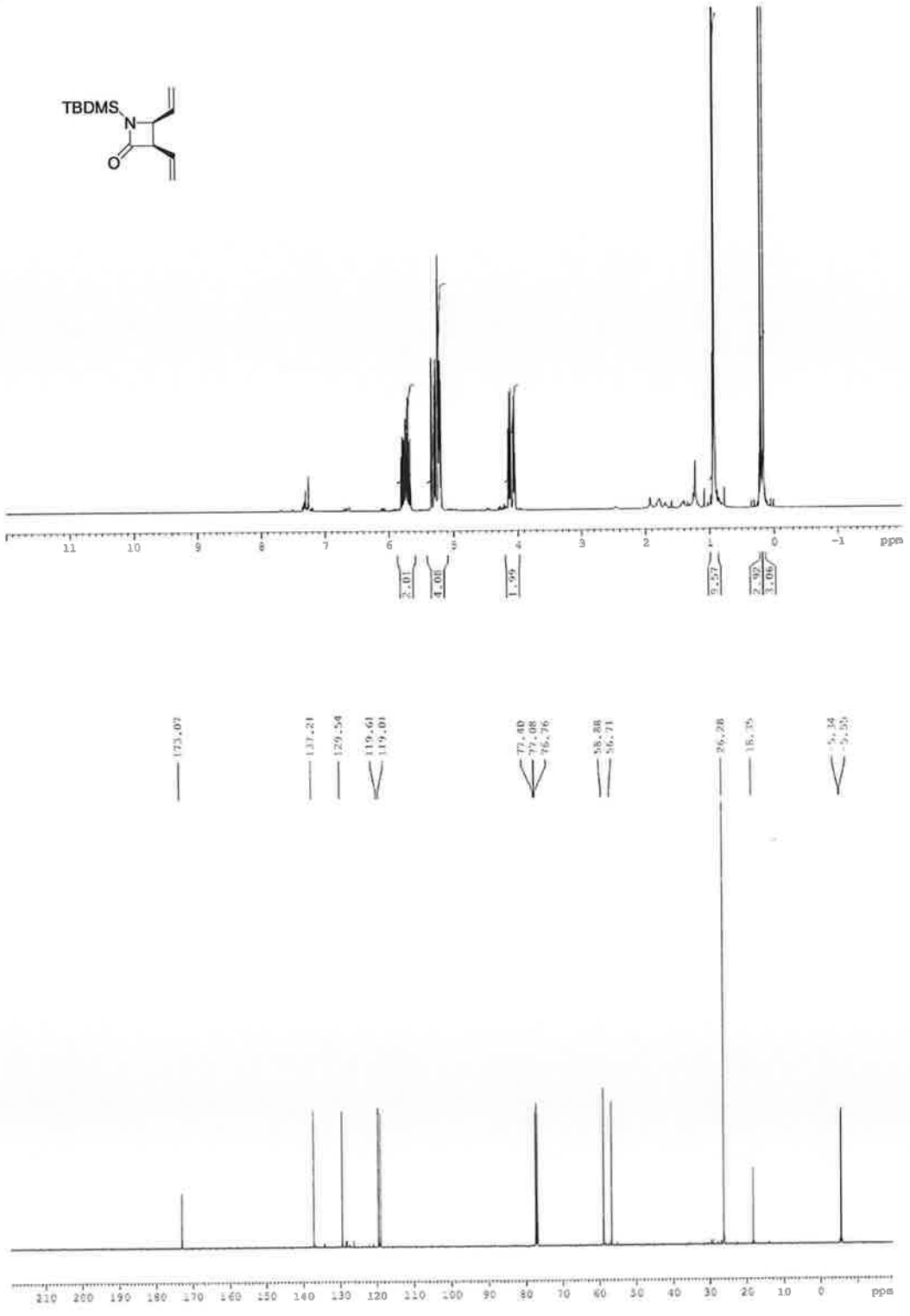


Compound 4.23

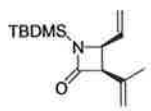


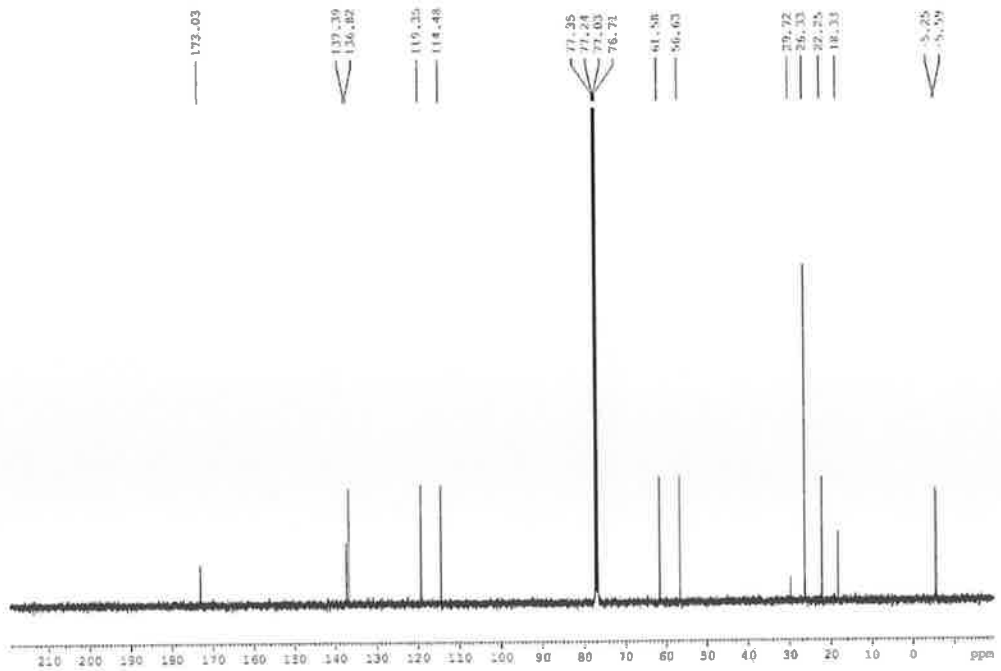


Compound 4.26

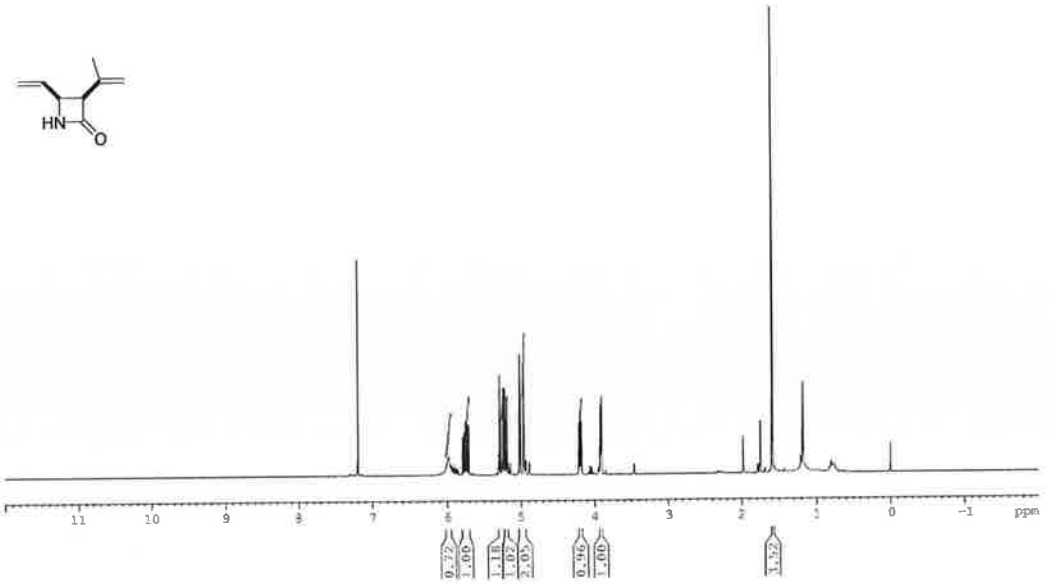


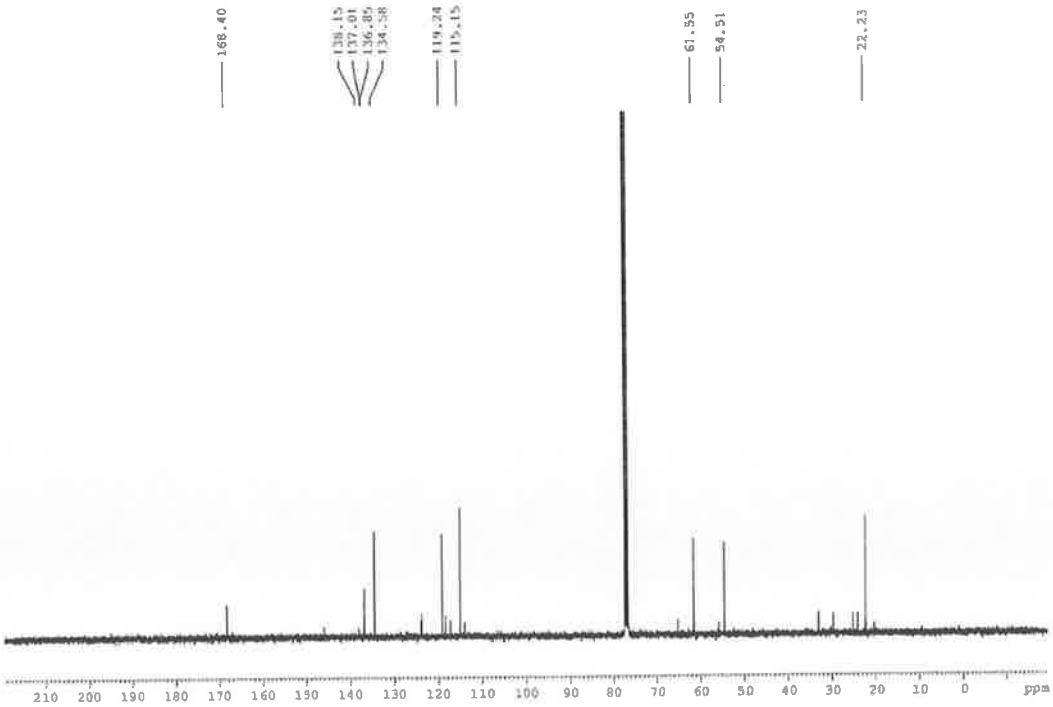
Compound 4.29





Compound *cis*-4.30





Compound *trans*-4.30